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This thesis analyzed and improved the kinetic index measure (Thomas, et al., 1994) by utilizing laboratory biological data to increase the validity of the parameters of an existing model. Then, using this "improved" model, raw magnetic field exposure data from a previous study was analyzed and compared with the measurement method used in that study (average magnetic field).

The results of the model modification showed that accurate modeling of the existing laboratory data could only be accomplished by including and additional parameter to the existing Litovitz multistage model. The results of the model application, however, were not particularly conclusive. The case-control study used for the model application was less than ideal, requiring that more rigorous epidemiological studies be conducted in order to accurately test the improved model.

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THESIS

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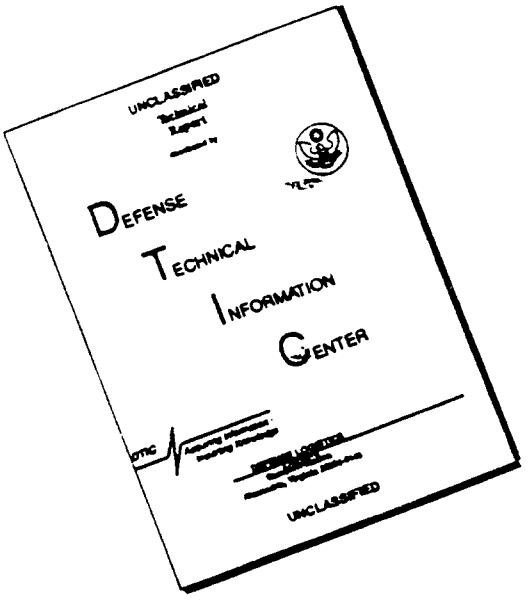


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AFIT/GEE/ENY/95D-01

# Modified Model For Transient Response Of mRNA Synthesis To Magnetic Field Exposure And Its Correlation To Adult Leukemia

THESIS

Presented to the Faculty of the School of Engineering of the
Air Force Institute of Technology
Air University
In Partial Fulfillment of the Requirements for the Degree of
Master of Science

Timothy W. Crosnoe, B.S., P.E.
Captain

December 1995

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Timothy W. Crosnoe

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## *Abstract*

It is a well known fact that high frequency, or radio frequency, radiation can be directly harmful to biological tissue. The radiation frequencies to which humans are most exposed, however, are the extremely low frequencies, or ELFs. To date there has been no definitive measure for predicting the ability of low frequency electromagnetic radiation to cause adverse biological effects. Two specific measures, average magnetic field and kinetic index, have been used in studies to determine if they are useful predictors of adverse effects, specifically leukemia. Unfortunately, both have shown only marginal results.

This thesis analyzed and improved the kinetic index measure (Thomas, et al., 1994) by utilizing laboratory biological data to increase the validity of the parameters of an existing model. Then, using this "improved" model, raw magnetic field exposure data from a previous study was analyzed and compared with the measurement method used in that study (average magnetic field).

The results of the model modification showed that accurate modeling of the existing laboratory data could only be accomplished by including and additional parameter to the existing Litovitz multistage model. The results of the model application, however, were not particularly conclusive. The case-control study used for the model application was less than ideal, requiring that more rigorous epidemiological studies be conducted in order to accurately test the improved model.

# 1. Introduction

## 1.1 Background

There is little doubt within the scientific community that extremely low frequency (ELF) electromagnetic fields (EMF) can produce some types of biological changes. What is in dispute is what types of effects these EMFs have and whether or not they have the potential to adversely affect human health.

One type of model which has been proposed and attempts to address magnetic field-induced changes at the cellular level is the Litovitz multistage DNA transcription model (Litovitz, et al., 1990:297-312; Litovitz, et al., 1992:237-246). This model seeks to illustrate the effects of a low-intensity, pulsed, ELF on the transcription of messenger ribonucleic acid (mRNA) in terms of a three-stage process. Its prediction asserts that when a magnetic field is turned on and subsequently held at a constant level, the mRNA concentration initially increases and then decreases to some basal level. The rise-time of the peak concentration and the resulting peak concentration of mRNA both depend upon the initial field strength. If the field is changed, the modeled mRNA concentration can take a much longer amount of time to return to its basal level than if the field had remained energized at its previous level.

Litovitz ,et al., chose their model parameters based solely upon characteristics (not specific data) exhibited by the snapshot responses of several earlier laboratory experiments (Goodman, et al., 1983:1283-1285; Goodman, et al., 1986:23-29). These experiments measured timed mRNA responses after being exposed to one of several different types of electromagnetic waveforms. Litovitz also assumed pulsed EMFs for his

model rather than EMFs which were ubiquitous for the general population (i.e. 60 Hz continuous). Very recent research (Lin, et al., 1995), however, exposed cells to continuous, interrupted, and changing 60 Hz fields. This data is to be used in this research to improve upon the Litovitz model.

### *1.2 Problem, Objectives, and Scope*

The major problem with ELF-EMF exposure is that to date there has been no solid statistically plausible antecedent-consequence relationship drawn between these exposures and incidents of leukemia. Upon reading Chapter 3 one will see that the only developed antecedents that have maintained a statistical correlation with ELF-EMF exposure are the Wertheimer-Leeper wiring codes. These codes assign exposure categories based upon the wiring configurations, mainly high-voltage distribution, surrounding the individual or population being tested. The coding is a partially subjective process, and, therefore, scientists are attempting to find a measure which will both provide good correlation and be objective.

One objective measure which would be the obvious first-choice is the average magnetic field exposure. After all, this, along with incidents of leukemia, can be measured directly and would intuitively seem to be the best choice. London, et al., in 1994 conducted a case-control study (Section 3.2 and Chapter 5) hoping to show just such an antecedent-consequence relationship. Although the point estimates for the odds ratios were higher, the confidence intervals were too wide to give this the required level of statistical assurance.

The Litovitz multistage model is the basis for another candidate objective measure. The drawback to this measure, however, is two-fold. First, and foremost, the model parameters used in creating this measure were not based on any specific biological data. They were chosen to show the subjective characteristics which had been discovered in earlier cellular experiments. In the one study which was conducted using this measure, model and its initial parameters as the basis for an exposure metric (Thomas, et al., 1994), the researchers were not able to show a correlation between the calculated metric and incidents of childhood leukemia (section 3.6).

This research will propose yet another possible predictor for leukemia incidents. This measure will be developed by modifying the existing Litovitz model parameters including the possible addition of parameters, in order to better represent mRNA responses. This will be accomplished by using the biological data from Lin, et al., 1995. Upon developing the modified model we will then use this model to predict mRNA synthesis from a data set taken of EMF-exposed individuals in the workplace. Finally, we will use these predictions to calculate real world occupational risk analysis figures which will hopefully show an improved antecedent-consequence relationship between ELF-EMF and incidents of leukemia in certain occupational groupings.

The potential connection that this model has with cancer formation is in the altered mRNA production. Cancer, in its most simplistic definition, is the uncontrolled reproduction of abnormal cells. As the next chapter will point out, mRNA plays a pivotal role in cell reproduction. If the Litovitz model is correct, and mRNA concentration rapidly increases upon exposure to ELF-EMFs, then it is entirely possible that these fields

could, at the very least, accelerate the reproduction of existing abnormal cells, and may actually contribute to the formation of abnormal cells.

### *1.3 Assumptions*

There are three main assumptions that deal directly with the Litovitz multistage model and are also foundations of the modified model. First, "there is some kind of biological transient response to an impressed EMF-ELF field." Second, "there is a maximal response that increases proportionally with the strength of the irradiating field." Finally, "there is a peak location that shifts to an earlier time as the field strength is increased" (Litovitz, et al., 1990:298). Additional assumptions proposed by Litovitz, et al., and maintained throughout the course of this research are:

> 1. Exposure to an EMF-ELF will increase both the synthesis and degradation rates in the multistep model (Figure 3 and Figure 4) (Litovitz, et al., 1992:241).
>
> 2. Reactions (Figure 3 and Figure 4) are strongly biased in the forward direction, and that only these rate constants (with the addition of any parameters added by this research) need be considered (Litovitz, et al., 1990:299).
>
> 3. The nucleotide reservoir will be rapidly replenished ([A] in Figure 4) (Litovitz, et al., 1990:300). [This means that the supply of nucleotides with which to maintain mRNA synthesis will be limitless].

# 2. Fundamentals

This chapter presents a review of the principles and characteristics of magnetic fields and a few proposed and established biological effects exhibited by them. It will also describe deoxyribonucleic acid (DNA) and mRNA as well as the role mRNA plays in transcribing DNA protein. In understanding these concepts one should be able to follow the background and development of the modified model which this thesis addresses.

## 2.1 Magnetic Fields

While electric fields are created by the existence of electric charges, magnetic fields exist only when those charges are moving. The force exerted on a moving charge by a magnetic field is given by the equation:

$$\mathbf{F} = q(\mathbf{v} \times \mathbf{B}) \tag{1}$$

where **F** is the force, q is a unit charge, **v** is the magnitude and direction of the relative motion of the field and **B** is the magnetic flux density. The unit of measure which will be used to describe the magnetic flux density is the milligauss (mG).

Normally it is unusual to find references which single out magnetic fields. They are typically referred to in combination with electric fields in a quantity known as electromagnetic radiation. In most situations these two fields travel in tandem and are considered as a single entity when studying the effects on living tissue. In the higher frequency ranges such as those involving radio, television, light, and microwave ovens this is the case. It is also the case that at these higher frequencies electromagnetic radiation has a thermal effect on biological tissue. However, in the lower frequency

ranges, such as those associated with the transmission and distribution of electrical power, electric fields and magnetic fields can, and almost always are, considered separately and do not outwardly appear to have an effect on the human body. The distinction between these two frequency groups is well established: "When the distance from a source of electromagnetic energy is large compared to the wavelength, the electric and magnetic fields are linked and are considered together as a single field. When the distance from the source is small with respect to the wavelength, the electric and magnetic fields are not linked and can be considered as separate entities" (EPRI, 1989:4).

The separation of these fields at low frequencies allows the investigation of the individual effects of exposure from each component field. The consensus of the scientific community is that most biological effects which are allegedly associated with extremely low frequency (ELF) electromagnetic fields (EMF) are most likely due to the magnetic component (Hileman, 1993:18). The reason for this is two-fold. First, trees, building materials, and clothing inadvertently shield the human body from most electrical field exposures. Second, the body itself is able to attenuate electric fields significantly due to its composition. The field transmitted to the inside of the body as a result of this attenuation tends only to be one millionth to one hundred millionth of the applied field (Hileman, 1993:18).

Magnetic fields, on the other hand, pass through biological material unimpeded. This occurs due to the lack of magnetic materials in living organisms. Additionally, any voltage gradients created across cell walls by magnetic fields are insignificant compared to those created by the cells' endogenous thermal fields. The highest voltage gradient

which can be initiated by a 60 Hz magnetic field (1,000 to 5,000 mG) across a cell wall is in the neighborhood of 50 volts per meter. The natural gradients across those same cell walls averages $10^7$ volts per meter (Hileman, 1993:19). Finally, magnetic fields do not have enough energy to heat tissue or disrupt DNA directly (Hileman, 1993:25). Considering the lack of magnetic material in the human body, the relatively insignificant voltage gradients created by an exogenous field, and the low energy of magnetic fields, it would be logical to conclude that magnetic fields should have little or no effect on biological systems.

Nevertheless, they have been shown to affect the synthesis rate of DNA through RNA transcription (Hileman, 1993:25). This phenomena, which will be described in detail later, has been studied and modeled by Litovitz, Montrose, et. al. (Litovitz et al., 1990:297-312) and forms a partial basis for the formulation of this paper's proposed model.

### *2.2 Natural and Typical Exposures*

All living things are exposed to a certain amount of constant electromagnetic energy which has been present ever since the earth was formed. One type is the static field which exists between the earth and the ionosphere (essentially a spherical capacitor). The most visible evidence of its existence is the occurrence of lightning which serves to equalize the charges. This field, however, is largely electric.

The other natural field which occurs is the geomagnetic field which is evident in the use of compasses. Like the capacitive field, it is largely static, oscillating slowly over

a 24-hour period, but in contrast it is largely magnetic. Its strength varies from 300 to 600 mG between the equator and the magnetic poles (Newman, 1992:1715).

Man-made sources of electromagnetic energy are numerous. High voltage power lines which receive the most scrutiny and are the most readily visible can produce magnetic fields of about 350 mG.

In the home, there are several sources of magnetic fields ranging from hair dryers to electric stoves. Fields in close proximity to these objects can be significantly higher than those found near high voltage lines. Table 1 below shows typical values of magnetic fields near several typical household appliances.

**Table 1 Typical Household Magnetic Exposures**

| Appliance | Magnetic Flux Density, mG | | |
|---|---|---|---|
| | 3 cm | 30 cm | 1 m |
| Can openers | 10000-20000 | 35-300 | 0.7-10 |
| Hair dryers | 60-20000 | 0.1-70 | <0.1-3 |
| Electric shavers | 150-15000 | 0.8-90 | <0.1-3 |
| Drills | 4000-8000 | 20-35 | 0.8-2 |
| Mixers | 600-7000 | 6-100 | 0.2-2.5 |
| Portable Heaters | 100-1800 | 1.5-50 | 0.1-2.5 |
| Blenders | 250-1300 | 6-20 | 0.3-1.2 |
| Television | 25-500 | 0.4-20 | 0.1-1.5 |
| Irons | 80-300 | 1.2-3 | 0.1-0.25 |
| Coffee makers | 18-250 | 0.8-1.5 | <0.1 |
| Refrigerators | 5-17 | 0.1-2.5 | <0.1 |

(EPRI, 1989:7)

Electrical distribution lines provide three specific sources of magnetic fields. Electrical currents in the primary feeders to service transformers create magnetic fields as do the secondary service drops from those transformers to residential or commercial customers. What is not normally considered, however, is the "net" field created by the vector sum of the secondary, primary, and neutral currents. This field's strength is

inversely proportional to the distance from the aggregate source while the field strengths of the primaries and secondaries are inversely proportionally to the square of the distance from their respective sources. This net field is not only stronger, but more uniform than those from its component fields.

Finally, many homes and businesses have electrical systems which are grounded to water pipes. This practice, though safe, produces non-uniform magnetic fields due to the return neutral current from home appliances. It also produces fields which vary greatly in time since the ground current changes every time a 120-V appliance is switched on or off (EPRI, 1989:8). In several studies investigating the effects of magnetic and electric fields on humans, the Midwest Research Institute (MRI) in Kansas City, Missouri consistently found that the greatest effects occurred just after the field was turned off or on (Hileman, 1993:24).

### *2.3 DNA, mRNA, and Protein Synthesis*

DNA is the basic genetic code of which all living things are constructed. It consists of two complementary chemical strands which are coiled around each other to form a double helix structure. The sequenced chemicals (or bases) making up the strands are called nucleotides. In DNA, nucleotides consist of a sugar and a phosphate group plus either of two purine bases adenine (A) and guanine (G) or either of two pyrimidine bases thymine (T) and cytosine (C). RNA is made up of the same basic units except that instead of T, it utilizes the pyrimidine uracil (U) (CIE, 1994).

The two sides of the DNA's double helix structure are held together by hydrogen bonds. Each base on a strand of DNA pairs only with its complement on the other strand.

G pairs only with C, and A pairs only with T (or with U in RNA). Each three-base set on a strand codes for a specific amino acid. The sequencing of these amino acids is the basis for protein synthesis (CIE, 1994).

Protein synthesis occurs in ribosomes which are located in the cytoplasm. DNA is located in the nucleus. Data needed for protein construction are transferred from the nucleus t the ribosomes via mRNA. mRNA is closely related to DNA and can carry genetic messages. In the transcription process DNA unwinds and separates its strands so that complementary strands of mRNA can be assembled on them. A strand of mRNA which has duplicated the DNA information then travels out of the nucleus to the ribosomes, where transcription of the actual DNA and protein synthesis begin. Since code transmission from DNA to mRNA is extremely Critical, any error in the code ultimately affects protein synthesis. If the error is serious enough, it eventually affects some body trait or feature of the subject organism.

# 3. Supporting Research and Model Development

The purpose of this chapter is to familiarize the reader with the existing biological research into the EMF-leukemia link, the EMF-biological systems link, the Litovitz multistage model which characterizes the biological link mathematically, and a study which has incorporated this model. Through the epidemiological studies this material should present a clear picture of the concerns EMFs present to the medical and scientific communities. It should next give sufficient background to allow comprehension of the laboratory experiments which have sought to directly link EMFs to specific biological effects. And finally, one should be able to understand the motivation and development of the current Litovitz multistage toxicokinetic model.

## 3.1 Residential Epidemiological Research

The most cited studies which cover the association of ELF-EMF exposures to cancer are a group of three childhood case-control studies, two in Denver, Colorado and one in Los Angeles, California.

The first study was conducted by Wertheimer and Leeper in 1979. In this study the authors designed their own exposure measurement system to approximate a measurement of long-term exposure. This system categorized homes according to characteristics of the distribution systems which supplied the homes with electrical power (e.g. conductor thickness and distance of conductor from the home). This study found that there was over a two-fold increase in the risk of brain cancer among children living in homes classified as "high-current" over those living in the "low-current"-classified homes (see Table 2). Additionally, the risk of contracting leukemia in high-current

homes was two to three times that of the low-current homes (see Table 1) (Wertheimer and Leeper, 1979:273-284).

The second Denver study was conducted in 1988 by Savitz, et al. In addition to using the Wertheimer and Leeper wiring system, Savitz, et al., also recorded short-term spot measurements of the electric and magnetic fields in various rooms throughout the homes. As Table 2 shows, when wiring classifications were used this study also showed a doubling of the brain cancer risk in the high-current homes when compared to the low-current homes. The risk of leukemia, however, was noticeably lower than the relative risks calculated in the first (Wertheimer and Leeper, 1979:273-284) Denver study (Table 3) (Savitz, et al., 1988:21-38).

The Los Angeles childhood leukemia study conducted in 1991 by London, et al., added an additional measurement to the second Denver study: 24-hour magnetic field measurements in the children's bedrooms (London, et al., 1991:923). This study, like the second Denver study, also showed a weaker association between the wiring configurations and childhood leukemia than the first Denver study. What the Los Angeles study did show, along with the second Denver study, is that there was no "consensus" among the various magnetic field measurements which would lead one to conclude that there was an association with cases of childhood leukemia (see Table 4). One implication which crosses all three studies is very important: the wiring configuration categories are not valid indicators of absolute levels of magnetic-field exposure (Trichopoulus, 1992:V-8).

**Table 2 RR of Childhood Brain Cancer in Relation to Wiring Configuration, High- vs. Low-Current Classifications (Case-Control)**

| Study | Residence Occupied | Relative Risk | 95% Confidence Interval |
|---|---|---|---|
| Wertheimer and Leeper 1979 | At time of birth<br>At time of death | 2.4<br>2.4 | 1.1-5.1<br>1.0-5.5 |
| Savitz, et al., 1988 | At time of diagnosis<br>2 years before diag. | 2.0<br>2.0 | 1.1-3.8<br>0.8-4.8 |

(Trichopoulus, 1992:V-3)

**Table 3 RR of Childhood Leukemia in Relation to Wiring Configuration, High- vs. Low-Current Classifications (Case-Control)**

| Location | Residence Occupied | Relative Risk | 95% Confidence Interval |
|---|---|---|---|
| Denver | At time of death<br>At time of birth | 3.0<br>2.3 | 1.8-5.0<br>1.3-3.9 |
| Denver | At time of diag.<br>2 years before diag. | 1.5<br>1.7 | 0.9-2.6<br>0.8-3.9 |
| Los Angeles | Longest in etiologic period | 1.7 | 1.1-2.5 |

(Trichopoulus, 1992:V-4)

**Table 4 RR of Childhood Leukemia in Relation to Four-Category Wiring Configurations (Case-Control)**

| Denver | | | Los Angeles | | | Los Angeles | | |
|---|---|---|---|---|---|---|---|---|
| Spot Measurement | | | Spot Measurement | | | 24-Hr Measurement | | |
| Measure & Category | RR | 95% CI | Measure & Category | RR | 95% CI | Measure & Category | RR | 95% CI |
| <0.65 mG | 1.0 | | <0.67 mG | 1.0 | | <0.68 mG | 1.0 | |
| 0.65-1.00 mG | 0.9 | 0.3-2.7 | 0.67-1.24 mG | 1.4 | 0.7-2.9 | 0.68-1.18 mG | 0.7 | 0.4-1.2 |
| 1.00-2.49 mG | 1.4 | 0.5-3.4 | 1.25 mG | 1.2 | 0.5-2.8 | 1.19-2.67 mG | 0.9 | 0.5-1.7 |
| ≥2.5 mG | 2.1 | 0.5-7.0 | | | | ≥2.68 mG | 1.5 | 0.7-3.3 |

(Trichopoulus, 1992:V-4)

In 1982 and 1987 Wertheimer and Leeper repeated their childhood experiment on adult subjects in the Denver area using the same methodology. They found that for all

cancers combined, the relative risk for high-current homes as compared to low-current homes was 1.4 with a confidence interval of 1.2-1.6 (Wertheimer and Leeper, 1982:345-355; Wertheimer and Leeper, 1987:43-53). Most of the other well-known adult studies which have been done (i.e. McDowall, 1986; Severson, et al., 1988; Youngson, et al., 1991; Meijers, et al., 1991), have either been accomplished with controversial methods or have not shown statistically significant associations between cancers and wiring configurations.

### *3.2 Occupational Epidemiological Research*

There have been many studies of occupational exposure to ELF-EMFs which have sought associations with various forms of cancer (i.e. leukemia, brain cancer, male breast cancer, etc.) (Trichopoulus, 1992:V18-V22). There have been so many, in fact, that it would not be practical to list them all here. The two forms of cancer which were the focus of most of these studies are the same as in the residential studies, i.e. leukemia and brain cancer.

In order to better view the overall research involving risks and exposure, Trichopoulus attempted to combine the findings of no less than 30 different epidemiological studies from 1963 to 1991 involving cancer and exposure to EMFs. These experiments included proportionate, case-control, and prospective/retrospective cohort studies (Trichopoulus, 1992:V29-V49). Their method of aggregating the experiments consisted of "estimat[ing] a summary proportionate mortality or incidence ratio for proportionate studies, a summary odds ratio for case-control studies, and a summary standardized mortality or incidence ratio for cohort or retrospective cohort

studies" (Trichopoulus, 1992:V-18). The specific methods used by Trichopoulus to calculate these summaries were as follows:

> "For proportionate and cohort studies, the observed and expected number of cases were obtained first for each study. The summary estimate was then calculated as the ratio between the sum of the observed cases and the sum of the expected cases. The aggregated estimate was therefore weighted proportionally to the size of the population. The 95% confidence interval for the summary estimate was obtained from a Poisson distribution (Rothman and Boice 1982).
>
> For case-control studies, the summary odds ratio estimate was derived from the weighted average of the logarithm of the odds ratio of the individual studies. The weights were taken to be proportional to the inverse variances of the log odds ratio. These variances were estimated from comparison of the upper and lower 95% confidence limits on the assumption that the difference between log upper and log lower confidence limits was 3.92 standard error of the log odds ratio. We calculated the 95% confidence interval of the summary odds ratio by taking the inverse sum of the weight as variance of the log summary odds ratio" (Trichopoulus, 1992:V-19).

The results of this composite of experiments can be found in Table 5 and Table 6 below.

**Table 5 Summary Analysis of Occupational Studies on EMFs and Leukemia**

| Leukemia Type | Design (n = observed cases) | Summary RR (95% CI) |
|---|---|---|
| All leukemia | Proportional mortality (n = 618) | 1.2 (1.1-1.2) |
| | Proportional Incidence (n = 148) | 1.2 (1.0-1.4) |
| | Case-control | 1.1 (0.9-1.3) |
| | Cohort (n = 599) | 1.1 (1.0-1.2) |

(Trichopoulus, 1992:V-20)

As one can see from Table 5, the relative risks for all leukemia ranged from 1.1 to 1.2, however, the only confidence interval which could assure a relative risk above 1.0 was that for the proportional mortality studies. These studies also yielded the "tightest" confidence interval among the four types.

Referring to the brain cancer summary table (Table 6), the case-control studies seem to show a fairly significant relative risk even considering the confidence interval. According to Trichopoulus, however, the hypothesis that these case-control studies were homogeneous had to be rejected. The proportional mortality summary relative risk also seemed to be a bit elevated, but it was only based on one study and still included 1.0 within its 95% confidence interval. Finally, the summary of the cohort studies did not show any tendency that the relative risk was different than 1.0.

What is interesting to note is that for both leukemia and brain cancer the widest confidence intervals are attached to the case-control studies. This would seem to indicate that one of the other types of studies would probably prove to be of more statistical value when planning new experiments.

**Table 6 Summary Analysis of Occupational Studies on EMFs and Brain Cancer**

| Design (n = observed cases) | Summary RR | (95% CI) |
|---|---|---|
| Proportional mortality (n = 110) | 1.2 | (1.0-1.4) |
| Case-control | 1.4 | (1.2-1.6) |
| Cohort (n = 429) | 1.0 | (0.9-1.1) |

(Trichopoulus, 1992:V-21)

One occupational study, however, needs some specific discussion. This is the 1994 study by London, et al., into leukemia risks encountered by electrical workers in the Los Angeles area (London, et al., 1994:47-60). The significance of this study is that it generated and analyzed the same data that is the subject of this research. The difference lies in the methods of analysis.

The subjects of this study agreed to wear magnetic field measuring/recording devices which would measure the rms magnetic field magnitude every 2.5 seconds of one

work shift. These values were then either averaged or surveyed for the percentage of time that an individual's exposure was over a predefined threshold value. The resulting values were used to create three exposure groups (London, et al., 1994:50). The table of interest is Table 7.

**Table 7 OR for Leukemia According to Estimates of Average Magnetic Field and Percent of Workday Above 2.5 and 25 mG by Occupation**

| Variable and Category | Cases | Controls | OR (95% CI) categorical | OR (95% CI) per 10 unit increase |
|---|---|---|---|---|
| Average Magnetic Field mG | | | | |
| <1.7 | 2264 | 65160 | 1.0 | |
| 1.8 - 8.0 | 61 | 1408 | 1.2 (1.0-1.6) | |
| 8.1 | 30 | 644 | 1.4 (1.0-2.0) | |
| All | 2355 | 67212 | | 1.2 (1.0-1.5) |
| Percent of time>2.5 mG | | | | |
| >13.0 | 2264 | 65160 | 1.0 | |
| 13.0 - 32.9 | 55 | 1131 | 1.4(1.1-1.8) | |
| 33.0 | 36 | 921 | 1.2(0.9-1.6) | |
| All | 2355 | 67212 | | 1.1 (1.0-1.2) |
| Percent of time>25 mG | | | | |
| <0.5 | 2268 | 65266 | 1.0 | |
| 0.5 - 7.9 | 57 | 1302 | 1.2 (1.0-1.6) | |
| >7.9 | 30 | 644 | 1.4 (1.0-2.0) | |
| All | 2355 | 67212 | | 1.4 (1.0-2.1) |

(London, et al., 1994:54)

This research showed a trend that electrical workers were at a slightly higher risk than non electrical workers, but because of the width of the confidence intervals the statistical association was not very strong.

### *3.3 Laboratory Research Supporting Cell Response Theories of Transiently Augmented Transcription*

Significant laboratory research has also been conducted which reports noticeable effects on various biological properties as a result of externally applied EMFs. First, certain low-frequency, sinusoidal EMFs increase mRNA transcription rates (Litovitz, et

al., 1990:297). Second, when such a sinusoidal external field is applied and subsequently remains constant, the mRNA response rises to some maximum value and then decays to a steady state value which depends upon the strength of the exogenous field (Litovitz, et al., 1990:298). Additionally, the magnitude and rise time of this maximum response have been shown to depend upon the strength of the applied field. As the strength of the field increases, the maximum of the response increases and the maximum occurs earlier in time. This response, however, does not increase without bound. Eventually a saturation point is reached and the maximum response will no longer increase with field strength (Litovitz, et al., 1990:298). Finally, supporting research has found that if such a field is prematurely terminated or its amplitude is modified, the return to a steady-state level can be greatly affected (Litovitz, et al., 1990:305-306; Lin, et al., 1995:1). These characteristics are modeled in Figure 1 and Figure 2.

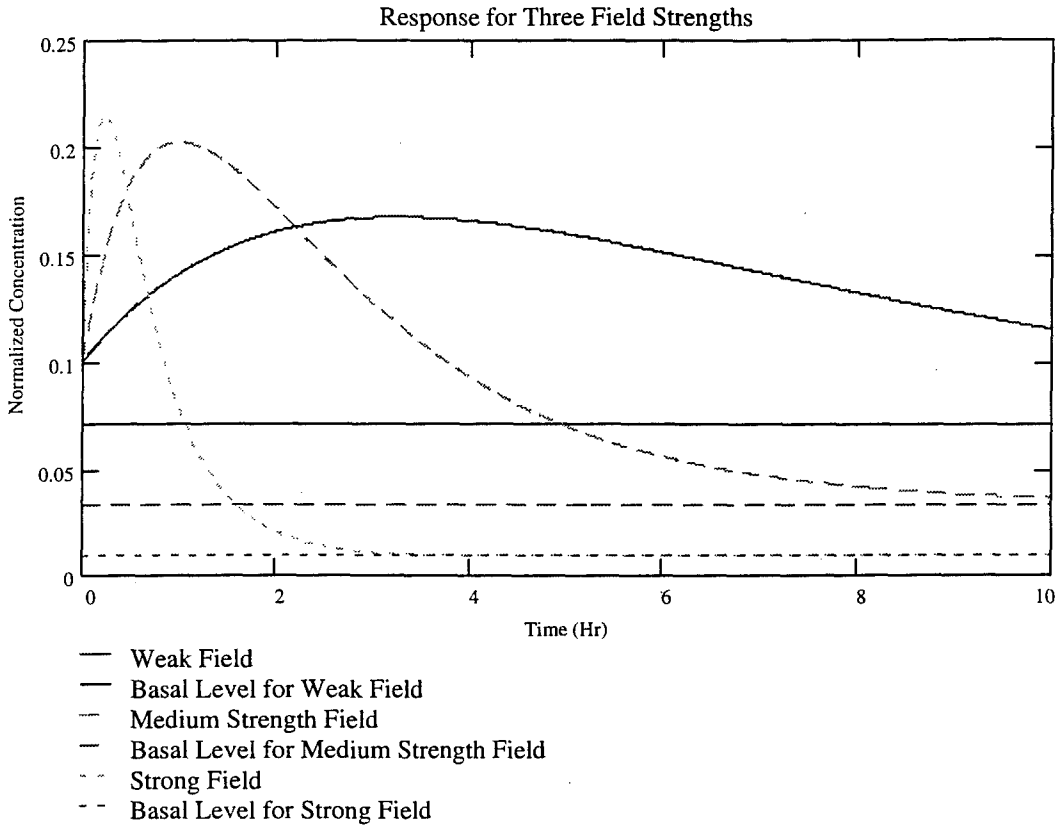



**Figure 1 Three Litovitz Model Transient Responses**

(Litovitz, 1990:302)

There is an additional property which is not necessarily obvious. This involves the fact that it is critically important to know at what point in time the response measurement is made when considering different field strengths. Looking closely at Figure 1, as time progresses the response to the strongest field actually falls below the responses of both the intermediate and weak fields before all three reach a lower steady-state value. This "moving" amplitude window makes timing critical when taking measurements of biological responses to electromagnetic fields. If, for example, a researcher were to record the affected biological activity at only the 4-hour mark, he might conclude, and incorrectly so, that the weakest field produces the largest response.

If data were recorded at the 90 minute mark, the medium strength field would be identified, again incorrectly, as the one producing the maximum response.

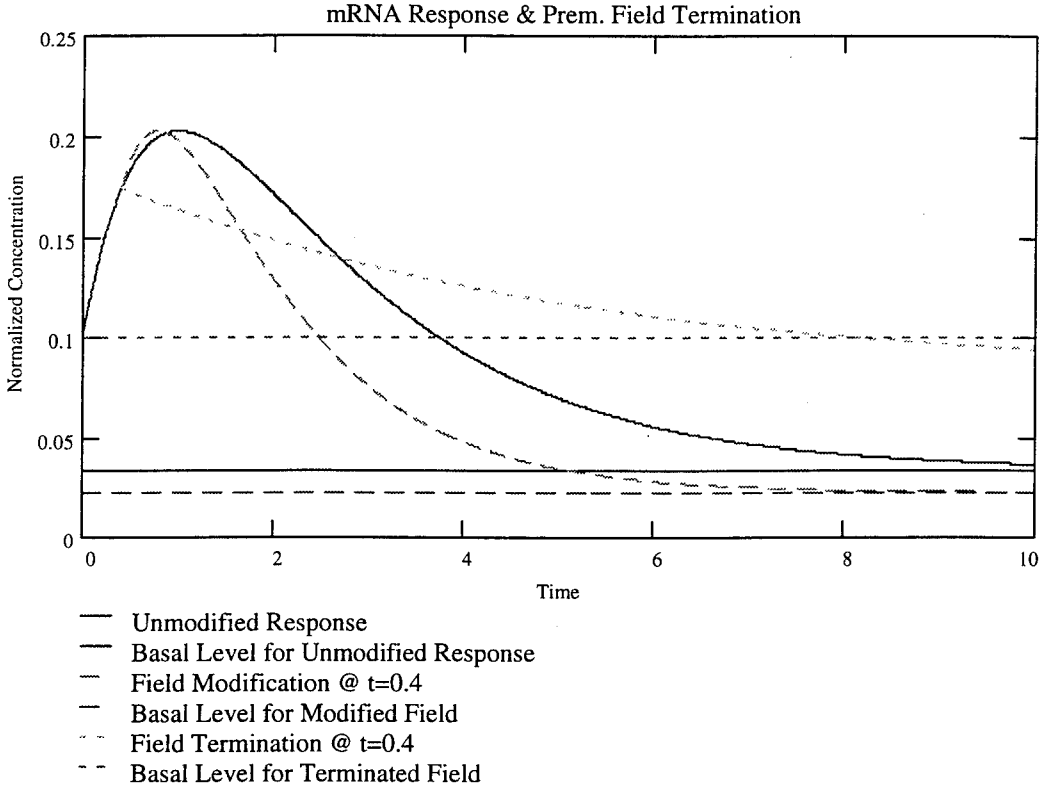



**Figure 2 Effects on Transient Response of Field Variation/Termination**

Responsiveness of mRNA transcription has been inferred qualitatively from observed systemic responses. For example, repetitive pulse train and repetitive single pulse EMFs of varying waveforms are used extensively to aid healing of stubborn bone fractures and in the treatment of avascular necrosis and osteoporosis (Goodman, et al., 1983:1283). To explore this directly at a cellular level, Goodman, et al., tested whether such EMFs had any effect on the normal RNA transcription patterns in the salivary gland chromosomes of the dipteran *Sciara coprophila*. Exposure to both types of quasirectangular, asymmetrical, pulsed EMFs resulted in increased transcription activity. However, the "effects of both pulses declined...after 60 minutes of continuous exposure"

(Goodman, et al., 1983:1283-1285) showing that the resulting augmented transcriptions were transient.

In 1986 Goodman and Henderson expanded this research to explore the effects of symmetrical sine waves on the transcriptional activity of *Sciara* salivary glands (Goodman and Henderson, 1986:23-29). Sine wave frequencies of 72, 222, and 4,400 Hz were applied at magnetic field strengths of 11,500, 3700, and 180 mG respectively. The 72 Hz signal was specifically chosen to compare with a single pulsed signal having a repetition rate of 72 Hz similar to that used in the 1983 research. The experiments revealed that exposure to the 72 Hz sine wave increased transcription in the same size classes as those seen following exposure to 72 Hz single-pulsed signal. The 222 and 4,400 Hz frequencies produced the same general pattern of induced transcription, but not as noticeably as the 72 Hz field. In fact, the transcriptional activity showed an inverse correlation with the field frequencies. One possible explanation for this could have been the significantly lower magnetic field strengths of the 222 and 4,400 Hz frequencies, however the object of the research was to show how signal shape, and not necessarily strength, would affect cell transcription. The "results demonstrate[d] that electromagnetic fields within a specific frequency range, irrespective of wave shape, can affect transcriptional activity in cells" (Goodman and Henderson, 1986:28). More specifically, certain symmetrical sine waves as well as pulsed EMF signals induce increased transcription in cells transiently under a continuous exposure.

The next logical step was to verify that this augmented transcription could be duplicated in human cell experiments. In 1989 Goodman, et al., exposed human

leukemia HL60 cells to five different ELF electromagnetic signals: three pulsed asymmetric signals with different repetition rates (1.5, 15, 72 Hz) and two continuous sinusoidal waveforms of 60 and 72 Hz (Goodman, et al., 1989b: 216-220). The pulsed signals were included to compare with the earlier *Sciara* transcription results, the 60 Hz sine wave was added to approximate the environment created by the power system frequency, and the 72 Hz sine wave was included for comparison with its corresponding pulsed, asymmetric signal. The result in each experiment indicated that the highest transcription augmentation occurred when the HL60 cells were exposed to the sinusoidal signals, and of those two signals the 60 Hz field produced the greatest transcription activity (Goodman, et al., 1989b: 218). Additionally, an in-depth analysis of this research as a whole indicated that within groups of differing signal types, the magnitude of transcript response seemed to show a dependence upon field strength (Goodman, et al., 1989a; Goodman, et al., 1989b:216-220).

The dependence upon field strength along with exposure time was specifically addressed by Goodman, et al., in 1992. This experiment, which exposed human HL-60 cells to continuous sine waves of 60 Hz, found measurable increases in some transcript levels (Goodman, et al., 1992:19). They also found that the transcript levels which were affected began responding to the exogenous fields at times as early as four minutes and peaked at twenty minutes when cells were exposed to magnetic fields of 57 mG. Transcript levels decreased to near control levels at twenty minutes when exposed to magnetic fields of 5700 mG (Goodman, et al., 1992:23). These findings closely follow characteristics outlined at the beginning of this section. In this experiment the response

to the 57 mG field showed a transient increase which was dependent upon the field strength. Although not specifically addressed, the explanation for the seemingly unresponsive 5700 mG field also supports a transient response dependent upon field strength. The reason that the 5700 mG field decreased to control levels after twenty minutes follows from the fact that the stronger the field, the earlier the peak response occurs and the quicker the return to basal levels.

The most recent research is reported in a 1995 research paper by H. Lin, et al., currently pending publication in Bioelectrochemistry and Bioenergetics. The aim of this research was to determine the effects of both continuous and limited duration 60 Hz, 80 mG field exposures on HL60 mRNA transcription activity (c-myc) (Lin, H., et al., 1995: 1-17). The results showed that under a continuous exposure the c-myc transcription levels peaked after 20 minutes and returned to a lower steady-state (basal) level after 60 minutes. When the field was turned off after a 20 minute exposure, however, it took three times longer to drop to a steady-state level (Lin, H., et al., 1995:1). The significance of this research is that it was the first research which explicitly exhibited the aggregate properties outlined in the Litovitz multistage model. This model will be covered in section 3.5.

As noted, these properties were specifically targeted by Litovitz, et al., in 1990 when they proposed a multistage mathematical model linking magnetic field strength to mRNA transcription. Development and application of this model are the subjects of the next section. The adjustment of this model to represent the empirical results of Lin, et al., 1995 is, in part, the subject of this thesis.

### *3.4 Laboratory Research Supporting Effects of Field Coherence on Transiently Augmented Transcription*

Although augmented transcription has proven to be a result of ELF-EMF exposure, the specific exogenous signal characteristics which cause this to occur and the resulting cell response mechanisms which directly elevate transcription activity are not entirely known. One signal characteristic which has been proposed to affect a cellular response is coherence. Qualitatively, coherence is inversely related to the rate of change of amplitude or frequency. A perfectly coherent signal would have constant amplitude and frequency. Both amplitude and frequency coherence have been studied as factors in cellular response.

Byus, et al., in 1987 investigated the ability of low-energy 60-Hz EM fields to alter the activity of ornithine decarboxylase (ODC) which is an enzyme involved in cell growth. Although the intent of this research was not to specifically identify coherence as the agent responsible for the altered enzyme activity, it did serve as the springboard for the research that did target coherence. The results showed that "a 1-hour exposure to a 60-Hz EM field of an intensity of 10 mV/cm produced a 5-fold increase in ODC activity in human lymphoma CEM cells and a 2- to 3-fold increase in mouse myeloma cells relative to the unexposed cultures. [Further,] depending on the cell type, ODC activity increased during the 1-hour exposure period and remained elevated for several hours after the field exposure ended" (Byus, et al., 1987:1385).

In 1991, Litovitz, et al., conducted additional experiments using ODC response as the indicator. This time, however, the intent was to identify whether or not a certain field characteristic might be responsible for increased transcriptional activity. Realizing that a

cell's incoherent endogenous thermal field is several orders of magnitude larger than those of most coherent exogenous fields, Litovitz, et al., set out to determine whether or not a cell has the ability to discriminate between coherent and incoherent fields. They found that by varying the frequency between 55 and 65 Hz with at least 10 seconds at each frequency setting (coherence time), using a 100 mG field, and exposing the cell cultures for 4 hours, they were able to enhance ODC activity just as much as if the field had been left at 55 or 65 Hz for the full 4 hour period. If a coherence time of 5 seconds was used, ODC activity was at a level half way between the controls and the 10 second samples. If any coherence time smaller than 1 second (essentially incoherent) was used, no activity was detected (Litovitz, et al., 1991:864).

The implications of these results were tested in two additional papers: Litovitz, et al., 1994a, and Litovitz, et al., 1994b. In the first paper Litovitz, et al., tested whether or not the combination of an incoherent noise field and a coherent 60-Hz field could keep developing chick embryos from experiencing abnormalities which in earlier experiments occurred as the result of exposure to certain 60 Hz fields alone (Litovitz, et al., 1994a:105-113). In the second paper Litovitz, et al., explored whether or not enhanced ODC activity in L292 cell cultures could be diminished under similar conditions as the chick embryos (Litovitz, et al., 1994b:399-409). In both instances as long as the superimposed noise was comparable in magnitude with the EMF signal, the signal effects on the biological subjects could be eliminated (Litovitz, et al., 1994a:110; Litovitz, et al., 1994b:407).

### *3.5 Multistage Toxicokinetic Model*

The definition of the term toxicokinetic literally means the movement of poisons throughout a body. Although electromagnetic fields are not technically considered to be toxins, the resulting augmentation of mRNA transcription, if destructive, can be considered a toxin. It is in this way that a model linking EMFs and harmful side effects can be considered toxicokinetic.

In 1990 and 1992 Litovitz, et al., found that a multistage model produced an acceptable approximation of the properties that the laboratory data was revealing. More specifically, this was a set of sequential, first-order chemical reactions modeled by differential equations. In order to posit this model, however, a hypothesis was needed to explain the multistage mechanisms by which augmented transcription was achieved (Litovitz, et al., 1990:297-312). The multistage model incorporated with the chosen mechanisms can be visualized as follows:

$$\left[\begin{array}{l}\text{Nucleotide}\\ \text{reservoir}\end{array}\right] \xrightarrow{\text{Diffusion}} \left[\begin{array}{l}\text{Positioned}\\ \text{G, C, A, U}\end{array}\right] \xrightarrow{\text{Polymerization}} [\text{mRNA}] \xrightarrow{\text{Degradation}} \cdots$$

**Figure 3 Stages of the Litovitz Multistage Model**
(Litovitz,et al., 1990:299)

This is simplified for discussion:

$$[A] \xrightarrow[k_1]{} [X] \xrightarrow[k_2]{} [Y] \xrightarrow[k_3]{} \cdots$$

**Figure 4 Variables Representing the Litovitz Multistage Model**
(Litovitz, et al., 1990:299)

The nucleotide reservoir concentration, which is assumed to be limitless, is given by $[A]$. $k_1$ is the rate constant representing the diffusion-controlled migration to and the positioning and orienting of the various nucleotides from the cellular pool (described in

chapter 2 as A, G, C, and U). [*X*] is the concentration of positioned and oriented nucleotides preparing for transcription. $k_2$ is the polymerization rate (oriented nucleotides combining to form a transcripted mRNA chain) of the positioned and oriented G, C, A, and U nucleotides. The resulting response, or mRNA concentration, before degradation is given by [*Y*]. And finally, $k_3$ is the degradation rate of messenger RNA by cytoplasmic nucleases (enzymes that promote hydrolysis of nucleic acids, i.e. chemical process of decomposition) (Litovitz, et al., 1990:299-300).

This multi-step model would, in reality, consist of a number of complex individual processes, but the assumption here is that the inclusion of more steps would not change the outcome of the model and would only minimally affect the shapes of the response functions at the different EMF strengths (Litovitz, et al., 1990:299). The pivotal hypothesis in the model is that switching on the electromagnetic field at t = 0 produces a "sudden" increase in $k_2$ and $k_3$. The increase in $k_2$ and $k_3$ will be symbolized by $k_2$* and $k_3$* (Litovitz, et al., 1992:241).

If the assumption is made that [*A*], the nucleotide reservoir concentration will always remain high enough to supply the process, the first order sequence of reactions can be described by the following set of linear first order differential equations:

$$\frac{dx}{dt} = +k_1 A - k_2 x \tag{2}$$

$$\frac{dy}{dt} = +k_2 x - k_3 y \tag{3}$$

(Litovitz, et al., 1990:300)

Assuming the system is initially at equilibrium (i.e. $x = \frac{k_1 A}{k_2}$ and $y = \frac{k_1 A}{k_3}$), the predicted response to a step change in the ELF electromagnetic field $t = \mathbf{0}$ is:

$$y(t \le t^*) = \frac{k_1 A}{k_3^*}\left(\mathbf{1} + \frac{\Delta k_3}{k_3} e^{-k_3^* t}\right) + \frac{k_1 A}{k_3^* - k_2^*}\frac{\Delta k_2}{k_2}\left(e^{-k_2^* t} - e^{-k_3^* t}\right) \qquad (4)$$

where $\Delta k_2 = k_2^* - k_2$

and $\Delta k_3 = k_3^* - k_3$ (Litovitz, et al., 1992:241)

where t* is the future point in time that the field is changed.

Normalizing the three rate constants with $k_1$ and normalizing the time dependent concentrations of *X, Y,* and *Z* (x, y, and z) with the initial concentration in the nucleotide pool [*A*], one can graph the function requiring values for only $k_2$, $k_2^*$, $k_3$, and $k_3^*$. Following Litovitz, et al., the rate constants $k_2$* and $k_3$* are assumed to be linear functions of the imposed field strength (see equations 5 and 6).

$$k_2^* = k_2 + \delta k_2 \cdot B \qquad (5)$$

$$k_3^* = k_3 + \delta k_3 \cdot B \qquad (6)$$

Litovitz gives $k_2$ = 1/15 $hr^{-1}$, $\delta k_2 = 1.23 \frac{1}{hr \cdot mG}$, $k_3$ = 1/6 $hr^{-1}$, and $\delta k_3 = 0.333 \frac{1}{hr \cdot mG}$. These values, however were not derived. They were picked by Litovitz to approximate known qualitative results. Figure 1 shows representative responses for B = 0.2, 1.0, and 5.0 mG respectively.

There are two characteristics of this model which are not readily apparent from the graphs. One is the fact that the response does yield a maximum as a function of field

strength. In other words, there is a point where the response no longer increases as a result of field strength and any increase in the field strength-calculated parameters $k_2^*$ and $k_3^*$ will not further increase the concentration of mRNA (Litovitz, et al., 1992:243). The peak will, however, occur earlier as the field strength is increased. The other interesting behavior is that a certain critical time seems to exist which will cause significantly larger bio-effects than those of earlier or longer exposure times. For the constants used in Figure 1, the critical time is approximately one hour (Litovitz, et al., 1992:243).

This model also shows that quenching a field before the response has had a chance to settle at a basal level has a significant effect on the response. When the field is switched off, the response not only takes much longer to stabilize, it also tends to "undershoot" what will be its final steady-state value and then gradually increases to meet it (Litovitz, et al., 1990:307). When the field is switched off ( $t^* \rightarrow t$ ), the response function becomes:

$$y(t \geq t^*) = \frac{k_1 A}{k_3} + Be^{-k_2(t-t^*)} + Ce^{-k_3(t-t^*)} \qquad (7)$$

where the initial conditions are the values of x and y immediately before the field is terminated;

$$\Delta k_3 = k_3^* - k_3; \qquad B = -\frac{k_1 A}{k_3 - k_2}\frac{\Delta k_2}{k_2^*}(1 - e^{-k_2 t^*});$$

and $$C = -B - \frac{k_1 A}{k_3}\frac{\Delta k_3}{k_3^*}\left[1 - e^{-k_3 t^*}\right] + \frac{k_1 A}{k_3 - k_2^*}\left[e^{-k_2 t^*} - e^{-k_3 t^*}\right]$$

(Litovitz, et al., 1992:241-242)

This function is shown concurrently with others in Figure 2.

### *3.6 Recent Application of Multistage Toxicokinetic Model*

In 1994 research, which at the time of this writing is awaiting publication, Thomas, et al., reanalyzed data from a 1991 case-control study of childhood leukemia and electromagnetic fields in Los Angeles County (London, et al., 1991:923-937). They used the Litovitz multistage model to derive an exposure metric known as the "kinetic index" (the integral of the mRNA response over the course of the measurement period) for each child and then, using a variety of statistical analyses, investigated the correlation between this index and the incidents of childhood leukemia (Thomas, et al., 1994:1).

Magnetic field measurements (root mean squared magnitude) were taken at fifty-second intervals in 308 residences yielding 164 cases and 144 controls (Thomas, et al., 1994:5). Using Litovitz's representative values for the rate constants, $k_1$, $k_2$, $k_3$, $\delta k_2$, and $\delta k_3$, Thomas, et al., calculated a response function for each separate fifty-second interval using the final response value of the previous interval as the initial response value for the next. The kinetic index was then calculated by integrating over all of the interval response functions of a particular individual. This yielded a single kinetic index metric per child (Thomas, et al., 1994:8).

The most notable result of this research in the context of this thesis was that individually neither the calculated kinetic index nor the 50-second autocorrelation (a measure in many regression applications indicating when the error terms in time-series data are not independent) trend tests provided a statistically significant link to the childhood leukemia incidents. However, in a multiple logistic regression analysis where both factors were considered predictors, the individual trend tests for the kinetic index and the fifty-second autocorrelation showed a statistical link (Thomas, et al., 1994:22-23).

# 4. Toxicokinetic Model Modifications and Application

This chapter will accomplish three goals. First it will outline the ideas which were considered as modifications to the Litovitz Multistage Model. It will then chronicle the logic and rationale behind the chosen modifications to the Litovitz Multistage Model. Finally, the model will be developed and used to create kinetic index (Thomas, et al., 1994:1) values for each individual whose magnetic field measurements were taken in the London, et al., 1994 study (London, et al., 1994:47-60).

## 4.1 Coherence-Kinetic Model

Because of the strength of association between the 50 second autocorrelation and the kinetic index in the Thomas, et al., research, the idea to somehow combine the two ideas into one model seemed logical. One linking mechanism investigated in this research was posited by Dr. Joseph Bowman of the National Institute of Occupational Safety and Health (Bowman, 1995).

In 1991 Litovitz, et al., presented a coherence theory which he thought could help explain augmented cell transcription by magnetic fields. Realizing that endogenous thermal noise fields within cells themselves are much larger than most fields caused by exogenous sources, Litovitz, et al., tested whether or not cells have the ability to discriminate between incoherent thermal noise and weaker coherent (constant phase, frequency, and amplitude) exogenous fields (Litovitz, et al., 1991:863).

The test exposed cultures of murine L929 cells to 60 Hz magnetic fields of 10, 100, or 1000 mG for times ranging from 1 to 8 hours. The response of interest was the enhancement in activity of the enzyme ornithine decarboxylase (ODC) in the L929 cells.

This was measured in terms of the ratio of exposed to control activity (Litovitz, et al., 1991:864).

The link between augmented mRNA transcription and increased enzyme activity is direct. Enzymes are constructed from proteins. The rate of synthesis of a protein is proportional to the amount of its corresponding mRNA that is present, any increase in the amount of mRNA will subsequently result in an enhanced rate of protein production and, therefore, enzyme production.

The results of the Litovitz, et al., experiment showed that "application of [constant amplitude] fields for four hours but with [frequency] coherence times of 10 or 50 seconds [produced] enhancements in ODC activities. .....In contrast, for coherence times of 0.1 or 1.0 seconds [essentially incoherent] no enhancement of ODC activity was observed" (Litovitz, et al., 1991:864). Further results showed that "for the cell to respond to an ELF signal it is necessary for the exogenous field to maintain coherence for a minimum time interval greater than about [5] seconds, with full response requiring an interval greater than about 10 seconds" (Litovitz, et al., 1991:864).

In order to further explore these observations, in 1994 Litovitz, et al., conducted experiments to see whether or not superimposing temporally incoherent (both frequency and amplitude) magnetic fields onto coherent 60 Hz fields suppressed the ODC activity of exposed L929 cells (Litovitz, et al., 1994a:399-409). "It [was] concluded that the superposition of incoherent magnetic fields can block the enhancement of ODC activity by a coherent magnetic field if the strength, or rms amplitude, of the incoherent field is equal to or greater than that of the coherent field" (Litovitz, et al., 1994a:399). By curve-

fitting data from this experiment, Litovitz developed the following equation which describes ODC activity as a function of the noise-to-signal ratio (a measure of amplitude coherence):

$$[\mathrm{ODC}] = 1 + \frac{1.06}{1 + 76\left(\frac{N}{S}\right)^2} \tag{8}$$

where N = noise (rms) and S = signal (rms).

(Litovitz, et al., 1994a:405)

Figure 5 shows the relationship of the ODC activity ratio with the noise-to-signal ratio. The smaller the noise-to-signal ratio, the greater the amplitude coherence and the greater the resulting ODC activity will be. Unfortunately, this equation does not include a factor for frequency coherence, noted in Litovitz, et al., 1991 as an additional factor affecting ODC activity.

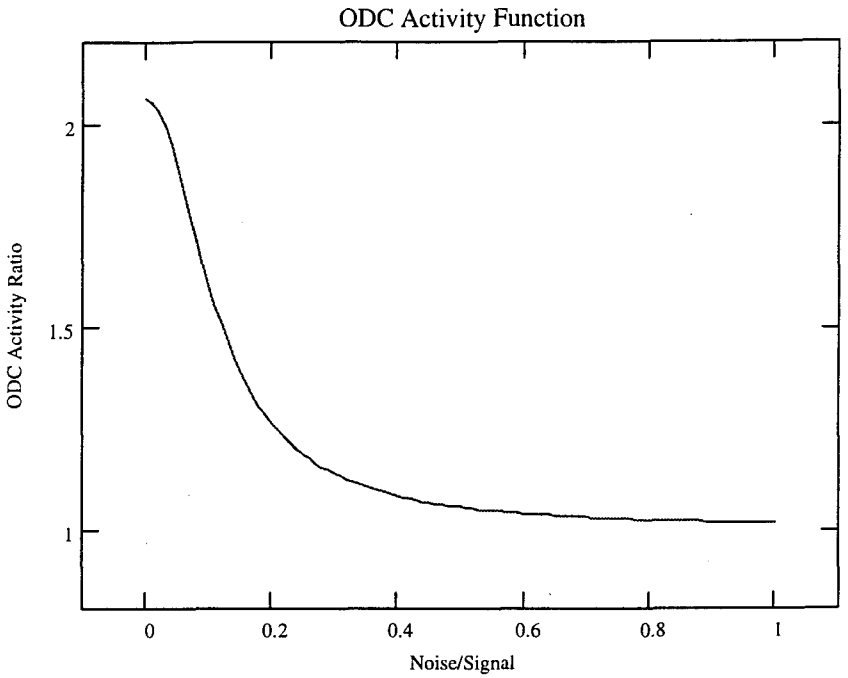



**Figure 5 ODC Activity Ratio vs. Noise-to-Signal Ratio**
(Litovitz, et al., 1994a:406)

As a result of the multistage model and the experiments relating coherence to enzyme activity, Dr. Bowman proposed combining the two models as the subject of this thesis. Originally this was to be accomplished by modifying the multistage rate constants using a factor which is controlled not only by the magnetic field strength, i.e. $k_2^* = k_2 + B \cdot (\delta k_2)$ hr$^{-1}$ and $k_3^* = k_3 + B \cdot (\delta k_3)$ hr$^{-1}$, but also by the coherence, i.e. $k_2^* = k_2 + B \cdot (\delta k_2) \cdot C$ hr$^{-1}$ and $k_3^* = k_3 + B \cdot (\delta k_3) \cdot C$ hr$^{-1}$, with coherence (C) being unitless (Bowman, 1995).

The data used in the London, et al., research in 1994 was taken by magnetic field meters which were worn by individuals representing various occupations for one duty day. The meters recorded magnetic field rms values (B) every 2.5 seconds (London, et al., 1994:49-50). In order to calculate a coherence factor from equation 8, a means of

computing noise and signal had to be established. Bowman proposed estimating the signal term by the moving average rms field value over the previous ten second period (four 2.5-second intervals). He did so because he interpreted the results of Litovitz, et al., 1991 to show that the minimum time for which coherence seemed to show noticeable effects on ODC activity to be 5 to 10 seconds (Litovitz, et al., 1991:864). The noise term would then be the difference between the moving average and the actual measured rms field value during the specific 2.5-second time increment of interest. Equations 9, 10, and 11 show specifically how these values were calculated.

$$\mathrm{SIGNAL}_i = \sqrt{\frac{1}{4} \cdot \sum_{k=i-3}^{i} \left[ B_{\mathrm{RMS}_k} \right]^2} \tag{9}$$

$$\mathrm{NOISE}_i = \sqrt{\frac{1}{4} \cdot \sum_{k=i-3}^{i} \left[ B_{\mathrm{RMS}_k} - \mathrm{SIGNAL}_k \right]^2} \tag{10}$$

(Bowman, 1995)

$$\mathrm{COHERENCE}_i = \frac{1.06}{1 + 76\left( \frac{\mathrm{NOISE}_i}{\mathrm{SIGNAL}_i} \right)^2} \tag{11}$$

(Litovitz, et al., 1994a:405)

Each $\mathrm{COHERENCE}_i$ term is represented by C in the linear rate constant equations that include coherence.

There were, however, a few of problems with this idea for a kinetic-coherence model. The first problem surfaced in Bowman's interpretation of the Litovitz, et al., 1991 results. Litovitz did not observe increased ODC activity after 10 seconds of exposure to an amplitude and frequency coherent field. What his results showed was that if an

amplitude coherent field varied its frequency in 10-second intervals or longer, e.g. oscillating between 55 Hz for the first 10 seconds and 65 for the next 10-second increment, for a period of **four hours**, maximum ODC activity would be observed after this four-hour period.

The second problem lay in the 1994 research by Litovitz, et al. This experiment was partially discussed earlier in section 4.1 and resulted in equation 8. Even though this equation is a fairly good predictor of the ODC activity ratio, the noise that was superimposed on the 60 Hz field not only was amplitude incoherent, it also varied frequency between 30 and 90 Hz. Granted, noise frequency fluctuations are more difficult to analyze, but since Litovitz, et al., had demonstrated in 1991 that this frequency variation could not be ignored, equation 8 should have reflected some sort of frequency dependence.

Even if Litovitz, et al., 1994 had measured and shown a frequency dependence, the data used in this thesis (London, et al., 1994) contained no frequency information other than the fact that the B-field readings were within the 40-400 Hz frequency range. With this in mind, frequency fluctuations could not be used to develop a modified multistage response model.

The final result, not really a problem, which was the decisive factor in discarding the idea to combine the kinetic index and coherence combination was revealed in a modeling comparison. When a sample data set for a single individual was used in both a model which included Bowman's suggested coherence term and a model which was the result of this research and did not include coherence, there were essentially no major

differences in model output. Figure 6 and Figure 7 below show that although the mRNA responses are not completely identical, they do indicate that the coherence term, when used in conjunction with smaller time constants, derived in this research, plays nearly no role when compared to a similar response model using only the smaller time constants.

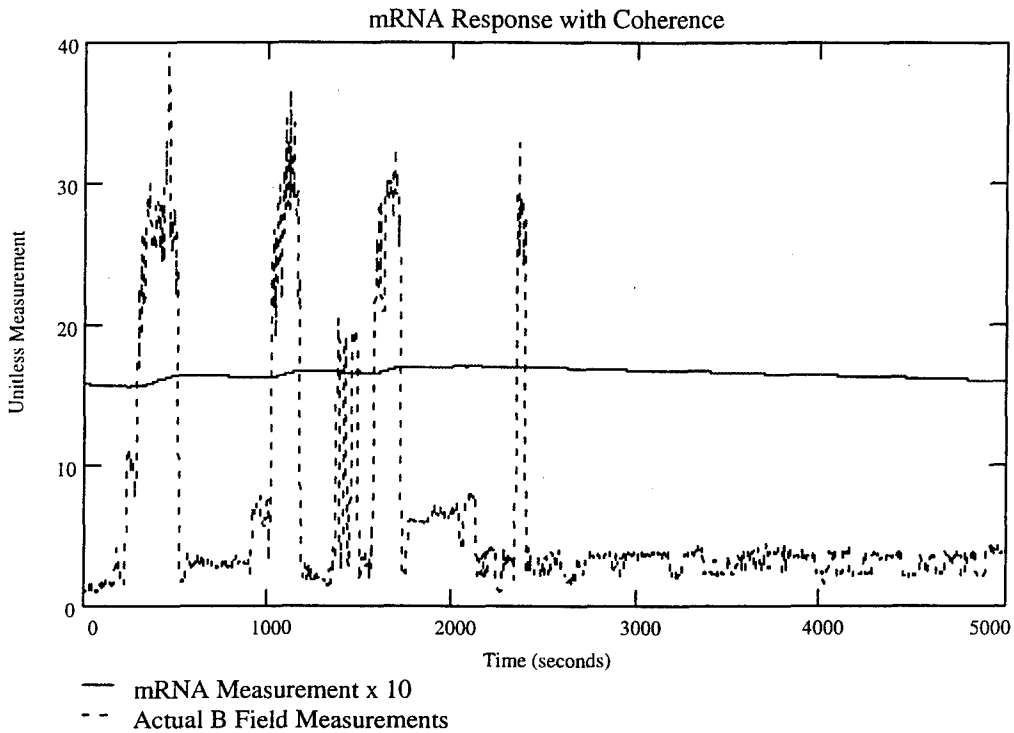



**Figure 6 Modeled mRNA Response with Coherence**

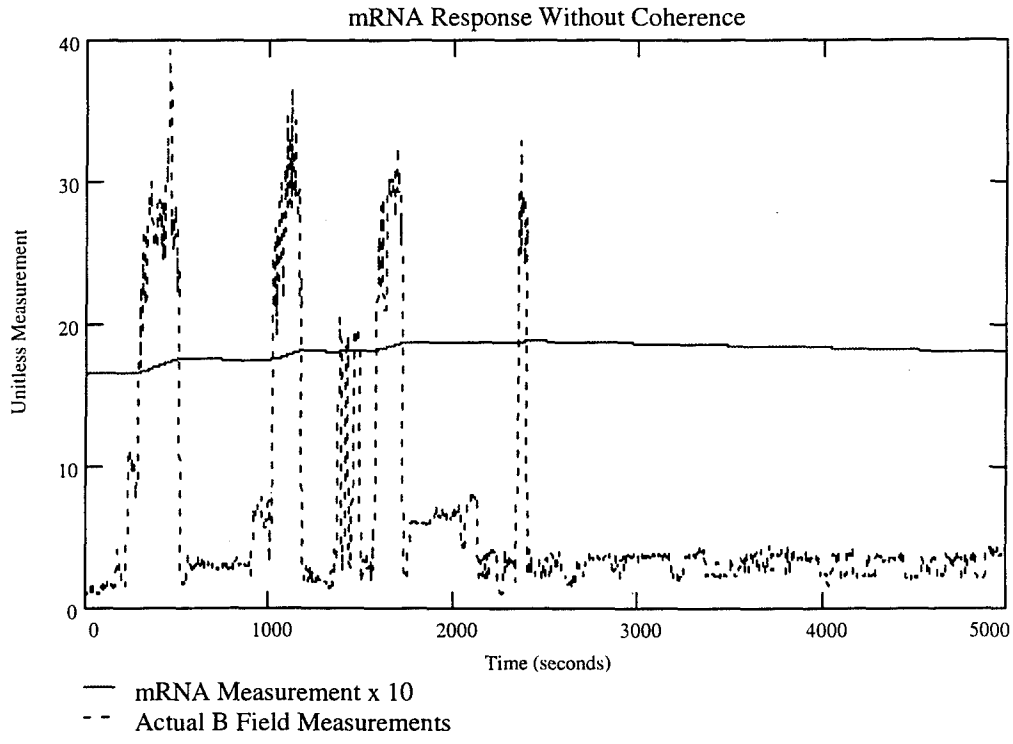



**Figure 7 Modeled mRNA Response without Coherence**

Since this specific combination of the coherence and kinetic models did not appear to be proper, from this point on coherence was not considered to be part of the model.

### *4.2 Modified Multistage Model*

During the research of this thesis Lin, et al., released results which seemed to directly support the characteristics demonstrated by the Litovitz multistage model. Their laboratory data was recorded under conditions of constant phase and frequency (60 Hz.) with the only varying factor being the amplitude (Lin, et al., 1995). This research reported complete response times which were on the order of one to two hours.

Since there was no laboratory data which specifically supported the numerical values of the multistage rate constants' chosen by Litovitz, et al., 1991 and 1992, the

focus of this thesis became the derivation of new rate constants for the Litovitz multistage model combined with an application of the resulting model to investigate leukemia incidents in certain Los Angeles County electrical occupations.

Using equation 4, normalized so that the steady-state ambient field response was 1, and the data points which were supplied by Lin, et al., 1995, we attempted to obtain values for $k_1$, $k_2$, $k_2^*$, $k_3$, and $k_3^*$. We found that by limiting the algorithm to only four degrees of freedom we could not obtain an adequate fit of a new function to the data points. This is clearly shown in Figure 8.

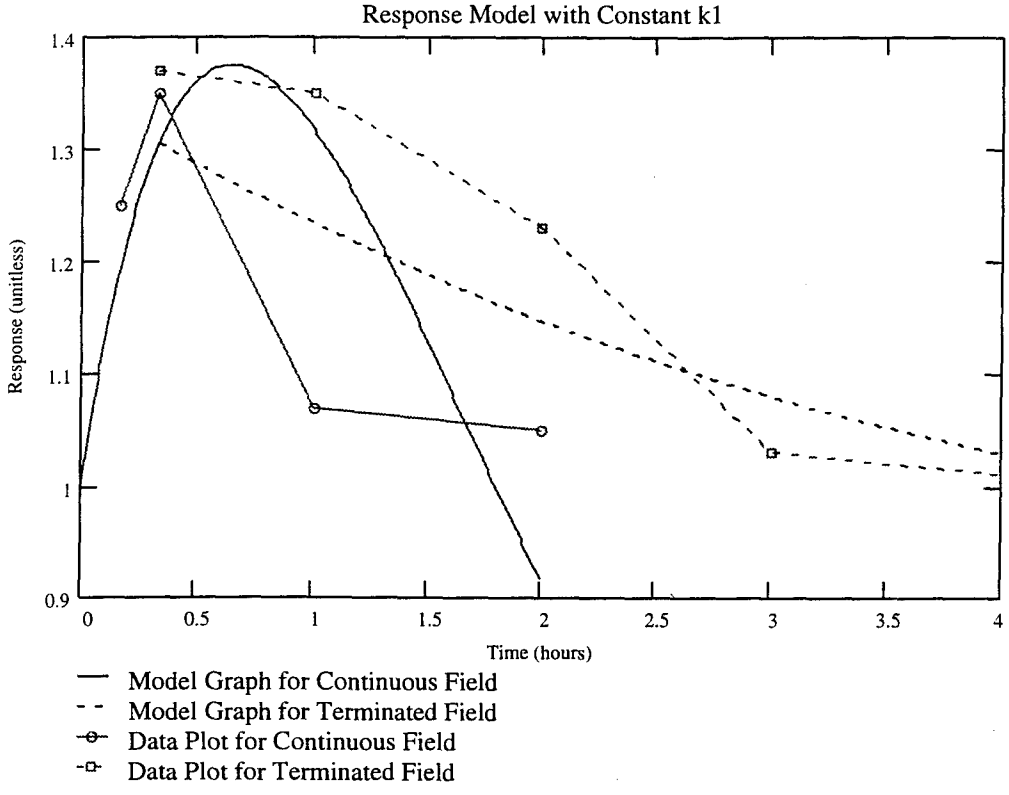



**Figure 8 Response Model Using Lin, et al., Data and Constant $k_1$**

An additional indicator suggested that this was an unrealistic fit of the data as well. The value for the rate constant $k_1$, which at this point had no corresponding $\delta k_1$

value, was an extremely large negative number, $k_1 = \frac{-5.196 \cdot 10^{98}}{60} sec^{-1}$. The other rate constants were on the order of $10^{-2}$ to $10^{-4}$ and were positive. Even given the speculative nature of the underlying physical model, this value of $k_1$ was completely unrealistic.

At this point, an additional question was added to the focus of the research. Could $k_1$, in addition to $k_2$ and $k_3$, also be accelerated by the presence of a magnetic field? This was a very logical question since both $k_2$ and $k_3$ both had corresponding $\delta k$ values By adding this new parameter, we were able to obtain an acceptable fit of the resulting function to the data points. The calculations of the new parameters are found in Appendices G and H. The plots of the data and resulting function are found in Figure 9. The parameters are:

$$k_1 = \frac{2.357 \cdot 10^{-4}}{60} sec^{-1} \qquad \delta k_1 = \frac{1.214 \cdot 10^{-3}}{60} sec^{-1} mG^{-1}$$

$$k_3 = \frac{1.965 \cdot 10^{-4}}{60} sec^{-1} \qquad \delta k_3 = \frac{7.152 \cdot 10^{-4}}{60} sec^{-1} mG^{-1}$$

$$k_2 = \frac{-1.383 \cdot 10^{-3}}{60} sec^{-1} \qquad \delta k_2 = \frac{7.361 \cdot 10^{-4}}{60} sec^{-1} mG^{-1}$$

and the rate constants for any interval, i = 1 to n, would be:

$$k_{1_i}^{*} = k_1 + B_i \cdot \delta k_1, \qquad k_{2_i}^{*} = k_2 + B_i \cdot \delta k_2, \qquad \text{and } k_{3_i}^{*} = k_3 + B_i \cdot \delta k_3$$

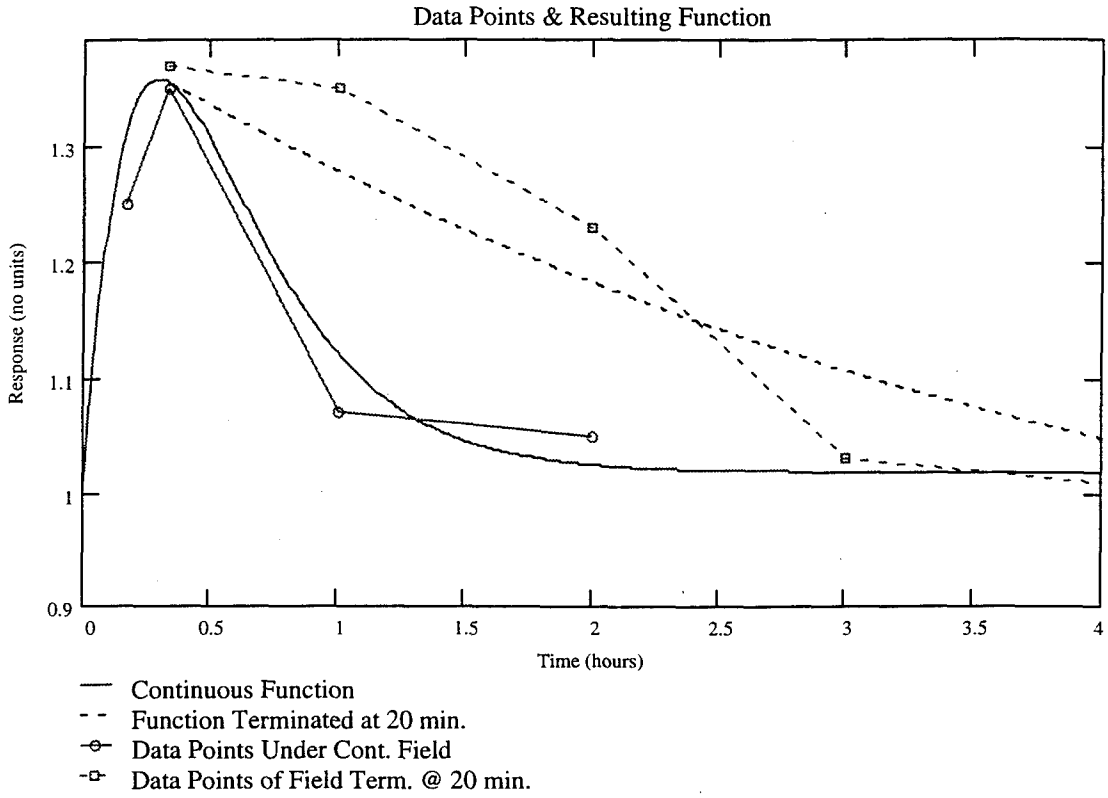



**Figure 9 Response Model Using Lin, et al., Data and Variable $k_1$**

It is interesting to note how much improvement was obtained by adding an additional degree of freedom to the model. One would intuitively expect improvement by adding a new parameter, but this improvement should be relative to the number of degrees of freedom. In this case the model has shown an unusually strong affinity to the additional parameter.

Based upon the original Litovitz model $k_1$ "represents the diffusion-controlled migration to, and the positioning and orienting of the various nucleotides from the cellular pool" (Litovitz, et al., 1990:299) along the DNA strands in the nucleus of the cell. One key assumption in the Litovitz model is that this part of the multistage process is passive and is unaffected by the presence of a magnetic field. However, as noted earlier,

this was a speculative assumption and is likely to be an oversimplification of the underlying biological processes. It is plausible, then, that $k_1$ may actually be affected by the presence of a magnetic field just as $k_2$ and $k_3$ are theorized to be.

On the other hand, this is still highly speculative. We know only that if a multistage model such as this is appropriate, then it must include variation of $k_1$ with the magnetic field. We also know that this multistage model exhibits all of the observed qualitative phenomena and fits the known quantitative data. The underlying mechanisms, however, are still unclear.

### *4.3 Application Procedure*

The next step was to use the new rate constants in the Litovitz multistage model to calculate the magnetic field responses, or kinetic indexes (Thomas, et al., 1994:1), for each 2.5 second interval for each individual in the London, et al., 1994 study. This was accomplished using a Matlab® program (see Appendix A for source code) incorporating a finite difference algorithm (see Appendix B). The output from this program will be analyzed in the next chapter.

# 5. Data Analysis

This chapter should enable the reader to understand how the output of the computer simulated model was calculated from the magnetic field data taken from the workers in Los Angeles. Additionally, one should comprehend the rationale and statistical bases behind the chosen statistical groupings. Next, odds ratio calculations, which were the ultimate result of the statistical analysis, should allow the reader to understand the conclusions which will be outlined in the next chapter. Finally, one should be able to distinguish the differences between using the average magnetic field and the kinetic index as indicators of exposure on identical data sets.

## 5.1 Kinetic Index Calculations

Although there has been some question during this research regarding the proper rate constants which should be used when applying the Litovitz multistage model, the model itself, as we have shown, is flexible enough to accurately represent the targeted biological properties with only slight modifications. This and the fact that the rate of change of the response function is almost negligible when considering only 2.5 second intervals led to a greatly simplified method of calculating kinetic indexes.

The following linear first order differential equations, (2) and (3), were first presented in chapter three (Section 3.5). Instead of using the solution to these equations to calculate the incremental responses from the data set, the responses were approximated at each interval by a set of finite difference equations (12) and (13).

$$\frac{dx}{dt} = +k_1 A - k_2 x \tag{2}$$

$$\frac{dy}{dt} = +k_2 x - k_3 y \tag{3}$$

(Litovitz, et al., 1990:300)

$$xx_{i+1} = xx_i + dt \cdot \left(k_1(b_i) - xx_i \cdot k_2(b_i)\right) \tag{12}$$

and $$yy_{i+1} = yy_i + dt \cdot \left(k_2(b_i) \cdot xx_i - k_3(b_i) \cdot yy_i\right) \tag{13}$$

where $k_1(b_i)$, $k_2(b_i)$, and $k_3(b_i)$ are the "starred" k values from section 3.5, each $b_i$ value is the magnetic field reading found in the $i^{th}$ recorded data interval, and dt = 2.5 seconds is the length of each interval. Once each $yy_i$ value was calculated, all were totaled for each individual and multiplied by 2.5 seconds in order to get an approximation for the time integral over the duty day (kinetic index). These individual indexes were then averaged over job codes representing the different occupations of the monitored individuals. The occupational kinetic indexes along with means, sample sizes, and standard deviations are found in Table 8.

**Table 8 Mean Kinetic Index and Associated Statistics by Occupation**

| Occupation | Mean K.I. ("dose"-minutes) | Sample Size | Std. Dev. | "Exposure" Group |
|---|---|---|---|---|
| Nonelectrical Worker | 410.74 | 95 | 144.50 | Low |
| Electrical Engineer | 439.41 | 14 | 179.17 | |
| Phone Line Worker and Splicer | 450.84 | 21 | 139.96 | |
| Electrician and Apprentice | 491.62 | 28 | 168.44 | Medium |
| Motion Picture Projectionist | 497.79 | 13 | 241.19 | |
| Electrical Engineering Technician | 507.97 | 11 | 128.30 | |
| TV and Radio Repairman | 568.28 | 19 | 173.73 | High |
| Electric Power Wire and Cable Worker | 585.43 | 87 | 148.40 | |
| Welder and Flame Cutter | 656.48 | 22 | 132.81 | |
| Power Station Operator | 686.76 | 34 | 135.49 | |
| Total | 523.22 | 344 | 152.95 | |

In order to show a comparison with the kinetic index we also calculated the average magnetic field exposure for each occupation. Even though this was the identical exposure indicator and data used by London, et al., 1994, it was not possible to use their figures directly because they task-weighted the averages. Since the report did not indicate how this weighting was accomplished, the averages had to be recalculated directly from the data. The occupational means, sample sizes, and standard deviations are found in Table 9.

**Table 9 Mean Average Magnetic Field Exposure and Associated Statistics by Occupation**

| Occupation | Mean Average Magnetic Field (mG) | Sample Size | Std. Dev. | "Exposure" Group |
|---|---|---|---|---|
| Nonelectrical Worker | 1.5081 | 95 | 1.0498 | Low |
| Electrical Engineer | 1.8478 | 14 | 1.8819 | |
| Phone Line Worker and Splicer | 1.9046 | 21 | 1.1355 | |
| Electrician and Apprentice | 2.91 | 28 | 1.9976 | Medium |
| Electrical Engineering Technician | 3.0778 | 11 | 2.3403 | |
| TV and Radio Repairman | 3.9836 | 19 | 2.6887 | |
| Motion Picture Projectionist | 7.918 | 13 | 7.0589 | High |
| Power Station Operator | 13.942 | 34 | 25.952 | |
| Welder and Flame Cutter | 17.059 | 22 | 24.376 | |
| Electric Power Wire and Cable Worker | 32.047 | 87 | 70.157 | |
| Total | 12.036 | 344 | 152.95 | |

### *5.2 Statistical Groupings, Tests, and Odds Ratios*

In 1994 London, et al., "performed a registry-based case-control study among men aged 20-64 years with known occupations who were diagnosed with cancer in Los Angeles County between 1972 and 1990" (London, et al., 1994:47). The case-control values from this study are found in Table 10. The raw data from the monitored subjects with which the case-control data were to be compared are the same used in this research. London, et al., however, used the average magnetic field as the "treatments" as opposed to the modified kinetic index derived in this research.

**Table 10 Cases and Controls by Category of Electrical Occupation Among Men Aged 20-64 and Diagnosed with Cancer in L.A. County, 1972-1990**

| Occupational Category | Leukemias (Cases) | Controls | "Exposure" Group |
|---|---|---|---|
| Nonelectrical Worker | 2234 | 64547 | Low |
| Electrical Engineer | 30 | 613 | |
| Phone Line Worker and Splicer | 4 | 31 | |
| Electrician and Apprentice | 28 | 728 | Medium |
| Motion Picture Projectionist | 1 | 22 | |
| Electrical Engineering Technician | 24 | 521 | |
| TV and Radio Repairman | 4 | 106 | High |
| Electric Power Wire and Cable Worker | 2 | 50 | |
| Welder and Flame Cutter | 27 | 579 | |
| Power Station Operator | 1 | 15 | |
| Total | 2355 | 67212 | |

(London, et al., 1994:54)

**Table 11 Mean K.I. and Associated Statistics by Occupational Grouping**

| Group | Mean KI ("Dose"-min.) | 95% CI ("Dose"-min.) | Sample Size | Group Std. Dev. |
|---|---|---|---|---|
| Low | 420.30 | 394.72 - 445.89 | 130 | 147.46 |
| Medium | 496.62 | 446.84 - 546.41 | 52 | 178.82 |
| High | 614.34 | 590.68 - 638.00 | 162 | 152.49 |

As with London, et al., we decided to use three groupings of occupational categories with the difference that they were grouped by average kinetic index rather than average magnetic field exposure. These groups were denoted as low, medium, and high "exposure." An attempt was made to ensure that each group would include at least thirty cases of leukemia. This was done so that there would be enough cases of leukemia to make statistically valid comparisons between the chosen groups. These groupings are found in both Table 8 and Table 10.

In order to assure that the three groupings were statistically different and had similar variances, two tests were accomplished. The first test was Bartlett's test of equal variances (see Appendix C). In this test the null hypothesis posited that the variances of all three groups were equal. The alternate hypothesis stated that not all variances were equal. With our kinetic index groupings, the p-value for the test was 0.2245 indicating that only if the significance level were greater than this could we reject the null hypothesis. We could, therefore, not reject the null hypothesis that all three variances were equal.

The second test was Tukey's pairwise comparison of means which would indicate whether or not the three groups had means which were significantly different from one another. Upon execution of the test we found that all three means were significantly different from one another at a rejection level of 0.050 (see Appendix C).

The final steps consisted of calculating the case/control ratios, the subsequent odds ratios and the confidence intervals for the odds ratios for all three groups (see Appendix E for calculations). Odds ratios and confidence intervals are shown in Table 12.

**Table 12 K.I. Odds Ratios and C.I.s by Occupational Grouping**

| Group | Odds Ratios | Confidence Intervals |
|---|---|---|
| Low Dose | 1 | N/A |
| Medium Dose | 1.199 | 0.9081 - 1.5821 |
| High Dose | 1.303 | 0.9227 - 1.8403 |

Alternatively, we also grouped occupations by average magnetic field exposure. This was the exposure metric used by London, et al., 1994, and the one which has not given consistent results. Again we chose three occupational groupings (low, medium,

and high) with an emphasis on including at least thirty leukemia cases in each group. These groupings are found in Table 9. Even though this was the best choice of several tested groupings, there were no low-medium-high groupings of occupations where Bartlett's test of equal variances was not rejected. Essentially, this meant that at least two groups of any chosen three based upon average occupational magnetic field exposure would not have variances which were statistically indistinguishable (see Appendix D).

There was also no combination which led to the finding of significantly different means between all three chosen groups (Appendix D). This was the most disconcerting finding in that if groups cannot be statistically separated, then any statistical calculations based upon them become meaningless. Statistics on the chosen groupings based upon average occupational magnetic exposure can be found in Table 13.

**Table 13 Mean Magnetic Field Exposure and Associated Statistics by Occupational Grouping**

| Group | Mean Magnetic Exp. (mG) | 95% CI (mG) | Sample Size | Group Std. Dev. |
|---|---|---|---|---|
| Low | 1.6088 | 1.4043 - 1.8132 | 130 | 1.1781 |
| Medium | 3.2935 | 2.6840 - 3.9030 | 58 | 2.3181 |
| High | 23.977 | 15.248 - 32.705 | 143 | 55.188 |

As with the kinetic index groupings, the final step was to calculate case/control ratios, odds ratios, and the confidence intervals for these odds ratios (see Appendix F). Odds ratios and confidence intervals are shown in Table 14.

**Table 14 Avg. Mag. Field Exposure Odds Ratios and C.I.s by Occupational Grouping**

| Group | Odds Ratios | Confidence Intervals |
|---|---|---|
| Low Dose | 1 | N/A |
| Medium Dose | 1.23 | 0.9433 - 1.6047 |
| High Dose | 1.338 | 0.9322 - 1.9202 |

One will immediately notice that the odds ratios of the medium and high groups of the average magnetic field measurement groupings are slightly higher than those of the kinetic index groupings (Table 12). The groupings for the average magnetic field measure, however, are questionable due to the fact that statistically separate occupational groupings could not be constructed using average magnetic field as the measure. In this case the inability to create statistically separate groupings may lead one to conclude, and not incorrectly so, that odds ratio calculations based on average magnetic field rather than the kinetic index are statistically invalid.

An interesting comparison exists between the two measurement methods' odds ratio confidence intervals. For both the medium and high groupings the separate measurement method confidence intervals have essentially the same widths. Here the explanation is not so much in the validity of the groupings as it is in the quality and numerical characteristics of the case-control data. Even though we compared two completely different measurement methods for EMF exposure, the same case-control numerical data was used for correlation purposes. Per grouping we did not significantly change the numerical values enough, between measurement methods, to adversely affect the widths of the confidence intervals.

Finally, we note the correlation between the kinetic index and the arithmetic mean of the magnetic field exposure for all of the monitored subjects. One will recall that Thomas, et al., 1994 used Litovitz's rate constant values and did not allow $k_1$ to vary in the analysis of its Los Angeles childhood leukemia data. In the Thomas research the correlation was almost perfectly negative ($\rho$=-0.97) using the log values (Thomas, et al.,

1994:25). The correlation using the London, et al., 1994 data set, allowing $k_1$ to vary, and using the rate constants derived in this research showed a nearly completely opposite trend ($\rho$=0.64), also using log values. This positive correlation makes physical sense, since we would expect that, if there is a biological response, generally greater magnetic fields should give generally elevated responses.

# 6. Conclusions

This final chapter should tie all aspects of this research together. By now the reader should have a good grasp on the rationale behind modifying Litovitz's multistage model as well as an understanding of how the changes were made. The conclusions and recommendations will be discussed in the areas of model development and model application separately.

## 6.1 The Improved Toxicokinetic Model

The most beneficial result of this research was the improvement of the Litovitz multistage model. Recent experimental data supplied by Lin, et al., 1995 allowed the Litovitz multistage model parameters to be calculated directly from biological data. Until this time, no calculation of parameters had been accomplished directly from biological data.

Of similar importance was the discovery that the biological data could be accurately modeled only by allowing all three of the time constants to vary with the imposed field. This required adding an additional parameter, $\delta k_1$. The assumption by Litovitz, et al., that $k_1$, described as diffusion-controlled positioning of the nucleotides (Litovitz, et al., 1990:300), does not change under magnetic field exposure was inconsistent with the Lin, et al., data. This could mean one of two things. Either the biological processes which Litovitz chose to explain the separate stages of the multistage model are not sufficient, which Litovitz, et al., have implied may be the case (Litovitz, et al., 1990:299), or diffusion controlled positioning of the nucleotides is indeed affected in

some manner by exposure to magnetic fields. More research will be needed to determine the proper conclusion.

Another suggestion for additional research would be another experiment to establish more data points for the transient behavior of mRNA concentration along the same lines as Lin, et al., 1995. Although there were sufficient data points to calculate the modified model parameters in this research, more data points would increase the confidence in the accuracy of the fit of the model. In particular, it would be useful to quantify the response in the first few minutes to help insure accurate modeling of changing fields.

### *6.2 Model Application*

One interesting difference between the kinetic index and the average magnetic field measures, is that slightly different occupational groupings were established by each. Taking a look at Table 8 and Table 9 one will find that the low groupings are identical in their occupational compositions. The medium exposure groups both contain electricians and electrical engineering technicians, but the third occupation is different. The average magnetic field exposure table (Table 9) contains the motion picture projectionist while the kinetic index exposure table (Table 8) moves this occupation to the high exposure group and replaces it with TV and radio repairmen from the average magnetic field's high exposure group.

Additionally, the occupations which are part of both high exposure groups, are not in the same order of ascending values. The average magnetic exposure shows power

station operators with the highest exposure, while the kinetic index yields electric power wire and cable workers as its highest exposure occupation.

The most noticeable result of the application of the modified Litovitz multistage model is the fact that the point estimates for the odds ratios using the kinetic index as the measure of exposure were not quite as high as those calculated using average magnetic field exposure. One would expect that they would be different due to the different methods of measuring exposure. The inability to create statistically separate groupings using average magnetic field as the measurement is another possibility. Another explanation, however, is that the average magnetic field metric may inflate the true odds ratios by encouraging inappropriate groupings.

The main reason that the application of the model developed in this research did not yield any more conclusive results (based on CI calculations) than did London, et al., in 1994 was due to the case-control type of epidemiological study conducted by London, et al. All of the subjects in the study were in a Los Angeles-based cancer registry. The cases were defined as those subjects who had leukemia. The controls were identified as those subjects with other forms of cancer (London, et al., 1994:48).

The first problem is that data begins with the bias that all participants had some form of cancer. Additionally, it is more than likely that these records were somehow historically incomplete thereby adding an additional element of bias. Finally, incidence rates, by the nature of a case-control study, are not available since no population-at-risk (total number of people who can develop disease or population at the beginning of a cohort study) has been defined. This effectively eliminates calculation of risk directly in

terms of the most desirable statistic-relative risk (the best epidemiological risk measure) and odds ratios become the best estimates of relative risk by default.

Most epidemiologists and statisticians would agree that either a prospective or retrospective cohort study would have narrowed the confidence intervals for both types of exposure measurements. A cohort study would also allow the calculation of relative risk rather than using the odds ratio as an estimate. Either way the statistical comparison of the two measurement methods would carry more weight. Although long term and expensive, a cohort study is the best way to improve upon this research.

### *6.3 Closing Comments*

The model developed in this research is definitely more appropriate for modeling cellular biological responses of exposure to low frequency electromagnetic fields. This is simply because data existed where it had not allowing a biologically valid model to be constructed.

It may initially seem that the modified kinetic index seems to be no better at measuring human system response to EMFs than the average magnetic field. This is due to nearly identical CIs and lower point estimates for the odds ratios. Actually, we believe it to be a more realistic measure due to its biological basis. With this in mind, the modified kinetic index becomes a more conservative measure of exposure (yielding lower odds) when compared to the average electromagnetic field, and supports the position that ELF-EMF exposure does not create as great of a biological effect as is currently hypothesized.

It will take much more research to establish whether or not the modified kinetic index is the best measure of ELF-EMF exposure, but one cannot ignore the validity of its

biological basis. One also has to consider the fact that no exposure metric to date has proven conclusive in predicting incidents of cancer. The fact that the modified kinetic index is a much more conservative approach to true exposure may help prove its validity indirectly as well.

# *Appendix A. Matlab Source Code for K.I. Calculations*

```
% A MATLAB M-file to process the EMDEX
% magnetic field exposure data from NIOSH.
%
% current(y,1)=IDENTIFICATION NUMBER
% current(y,2)=mG MAGNETIC FIELD LEVEL
% current(y,3)=JOB CODE OF THE INDIVIDUAL
% current(y,4)=REGION (i.e. 1=LA, 2=WA, 3=NZ)
% current(y,5)=k1(b)
% current(y,6)=k2(b)
% current(y,7)=k3(b)
% current(y,8)=xx concentration
% current(y,9)=yy concentration
%

clear;
format long e;
load mag.dat;
        % The original data file has been modified to only include the original
        % field values known as ID, M, BOC, and REGION.
        % The REGION field was modified as follows due to MATLAB's inability to
        % read ASCII data:
        %       LA = 1
        %       WA = 2
        %       NZ = 3

limit=max(size(mag))+1;
        % Needed to add one line (above) to the data file to compare last id # to.

mag(limit,:)=[0 0 0 0];
        % For the above purpose, I pick an arbitrary array value which will not
        % match the last individual's ID field.

scale=1/60;
        % This will change the output scale to dose-minutes.

x=1; binit=4;
        % binit is the ambient magnetic field level used in Dr. Reba Goodman's
        % experiment (4 mG).

k1=2.3574227589E-04*scale; delk1=1.2144280925E-03*scale;
k2=-1.3834909426E-03*scale; delk2=7.3608201871E-04*scale;
k3=1.9646532847E-04*scale; delk3=7.1523014986E-04*scale;
        % This sets all of the rate constants.
```

```
k10=k1+binit*delk1; k20=k2+binit*delk2; k30=k3+binit*delk3;
        % This sets the initial rate constants based on the ambient magnetic
        % field referenced above.

xx0=k10/k20;
yy0=k10/k30;
        % These are the initial values of the X and Y concentrations in the
        % multistage model as calculated from the ambient mag. field noted above.
cnt=0;

while x<=limit-1;
        % Pointer is at the first record in an individual's file

  y=1;
  cnt=cnt+1;
  kinetic(cnt,1)=mag(x,1); kinetic(cnt,2)=mag(x,3); kinetic(cnt,3)=mag(x,4);
  current(y,:)=mag(x,:);
  current(y,5)=k1+current(y,2)*delk1;
  current(y,6)=k2+current(y,2)*delk2;
  current(y,7)=k3+current(y,2)*delk3;
  current(y,8)=xx0+2.5*(k10-xx0*k20);
  current(y,9)=yy0+2.5*(k20*xx0-k30*yy0);
  x=x+1;
  y=y+1;

        % Pointer is at the second record in an individual's file.

  beg=x;
  while mag(x,1)==mag(x-1,1);
    x=x+1;
    y=y+1;
  end;
%x
%y
%beg
    current(2:
y,1:4)=mag(beg:x,1:4);
    current(2:y,5)=k1+current(2:y,2)*delk1;
    current(2:y,6)=k2+current(2:y,2)*delk2;
    current(2:y,7)=k3+current(2:y,2)*delk3;

  for i=2:y;
    current(i,8)=current(i-1,8)+2.5*(current(i-1,5)-current(i-1,8)*current(i-1,6));
    current(i,9)=current(i-1,9)+2.5*(current(i-1,6)*current(i-1,8)-current(i-1,7)*current(i-
1,9));
```

```
  end;
  kinetic(cnt,4)=(2.5/60)*sum(current(:,9));
%   save c:\school\thesis\current.dat current /ascii;
  clear current;
end;
save kinetic.dat kinetic /ascii;
```

# *Appendix B. Finite Difference Calculations*

Kinetic model

The differential equation will be approximated by coupled difference equations with time varying coefficients. The base time unit will be one second, and the output will be stored at dt second intervals. The imposed field will be interpolated between samples.

Pick up data $EMDEX := READPRN(magdata)$ $DEX := EMDEX^{<2>}$ $length(DEX) = 5.664 \cdot 10^3$

data every dt.data seconds $dt_{data} := 2.5$ $t_{max} := dt_{data} \cdot length(DEX)$ $t_{max} = 1.416 \cdot 10^4$

Set up rate constants $scale := \frac{1}{60}$

$k_{10} := 2.3574227589 \cdot 10^{-4} \cdot scale$ $k_{20} := -1.3834909426 \cdot 10^{-3} \cdot scale$ $k_{30} := 1.9646532847 \cdot 10^{-4} \cdot scale$

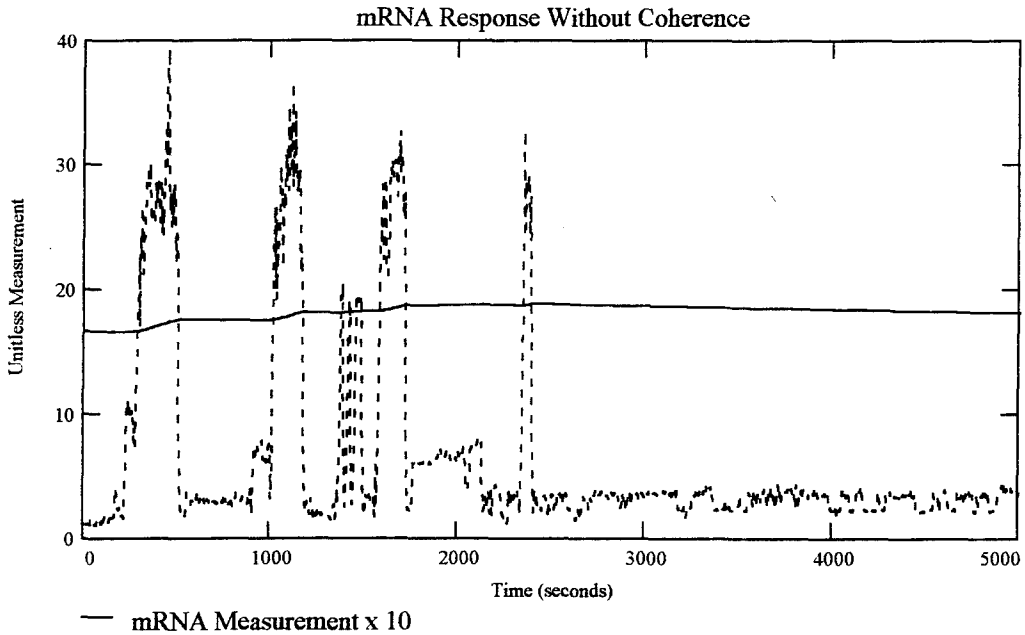
$\delta k_1 := 1.2144280925 \cdot 10^{-3} \cdot scale$ $\delta k_2 := 7.3608201817 \cdot 10^{-4} \cdot scale$ $\delta k_3 := 7.1523014986 \cdot 10^{-4} \cdot scale$

$k_1(b) := k_{10} + b \cdot \delta k_1$ $k_2(b) := k_{20} + b \cdot \delta k_2$ $k_3(b) := k_{30} + b \cdot \delta k_3$

Set up integration and storage parameters

$t_0 := 0$ $t_{final} := length(DEX) \cdot 2.5$ $n_{pts} := length(DEX)$ $i := 0 .. n_{pts} - 1$ $b_0 := 4$ $dt := 2.5$ $tt_i := i \cdot dt$

$$\begin{pmatrix} xx_0 \\ yy_0 \end{pmatrix} := \begin{pmatrix} \frac{k_1(b_0)}{k_2(b_0)} & \frac{k_1(b_0)}{k_3(b_0)} \end{pmatrix}^T \qquad \begin{pmatrix} xx_{i+1} \\ yy_{i+1} \end{pmatrix} := \left\| \begin{array}{l} b \leftarrow DEX_i \\ \begin{pmatrix} xx_i \\ yy_i \end{pmatrix} + dt \cdot \begin{pmatrix} k_1(b) - xx_i \cdot k_2(b) \\ k_2(b) \cdot xx_i - k_3(b) \cdot yy_i \end{pmatrix} \end{array} \right.$$



# *Appendix C. Kinetic Index Metric Statistics*

STATISTIX 4.1®  LA_DATA, 11/01/95, 13:20

ONE-WAY AOV FOR KI BY GROUP

| SOURCE | DF | SS | MS | F | P |
|---|---|---|---|---|---|
| BETWEEN | 2 | 2.759E+06 | 1.379E+06 | 57.50 | 0.0000 |
| WITHIN | 341 | 8.180E+06 | 23987.6 | | |
| TOTAL | 343 | 1.094E+07 | | | |

| | CHI-SQ | DF | P |
|---|---|---|---|
| BARTLETT'S TEST EQUAL VARIANCES | 2.99 | 2 | 0.2245 |

COCHRAN'S Q  0.4154
LARGEST VAR / SMALLEST VAR  1.4705

COMPONENT OF VARIANCE FOR BETWEEN GROUPS  12863.9
EFFECTIVE CELL SIZE  105.4

| GROUP | MEAN | SAMPLE SIZE | GROUP STD DEV |
|---|---|---|---|
| 1 | 420.30 | 130 | 147.46 |
| 2 | 496.62 | 52 | 178.82 |
| 3 | 614.34 | 162 | 152.49 |
| TOTAL | 523.22 | 344 | 154.88 |

CASES INCLUDED  344  MISSING CASES  0

TUKEY (HSD) PAIRWISE COMPARISONS OF MEANS OF KI BY GROUP

| GROUP | MEAN | HOMOGENEOUS GROUPS |
|---|---|---|
| 3 | 614.34 | I |
| 2 | 496.62 | I |
| 1 | 420.30 | I |

ALL 3 MEANS ARE SIGNIFICANTLY DIFFERENT FROM ONE ANOTHER.

CRITICAL Q VALUE 3.314  REJECTION LEVEL 0.050
STANDARD ERRORS AND CRITICAL VALUES OF DIFFERENCES
VARY BETWEEN COMPARISONS BECAUSE OF UNEQUAL SAMPLE SIZES.

# *Appendix D. Average Magnetic Field Metric Statistics*

STATISTIX 4.1®

LAAVGMAG, 11/01/95, 13:21

ONE-WAY AOV FOR AVG_B BY GROUP

| SOURCE | DF | SS | MS | F | P |
|---|---|---|---|---|---|
| BETWEEN | 2 | 40810.7 | 20405.3 | 14.72 | 0.0000 |
| WITHIN | 341 | 4.726E+05 | 1385.84 | | |
| TOTAL | 343 | 5.134E+05 | | | |

| | CHI-SQ | DF | P |
|---|---|---|---|
| BARTLETT'S TEST EQUAL VARIANCES | 1080.17 | 2 | 0.0000 |

| | |
|---|---|
| COCHRAN'S Q | 0.9978 |
| LARGEST VAR / SMALLEST VAR | 2194.6 |

| | |
|---|---|
| COMPONENT OF VARIANCE FOR BETWEEN GROUPS | 177.463 |
| EFFECTIVE CELL SIZE | 107.2 |

| GROUP | MEAN | SAMPLE SIZE | GROUP STD DEV |
|---|---|---|---|
| 1 | 1.6088 | 130 | 1.1781 |
| 2 | 3.2935 | 58 | 2.3181 |
| 3 | 23.977 | 156 | 55.188 |
| TOTAL | 12.036 | 344 | 37.227 |

CASES INCLUDED 344 MISSING CASES 0

TUKEY (HSD) PAIRWISE COMPARISONS OF MEANS OF KI BY GROUP

| GROUP | MEAN | HOMOGENEOUS GROUPS |
|---|---|---|
| 3 | 23.977 | I |
| 2 | 3.2935 | I |
| 1 | 1.6088 | I |

THERE ARE 2 GROUPS IN WHICH THE MEANS ARE
NOT SIGNIFICANTLY DIFFERENT FROM ONE ANOTHER.

CRITICAL Q VALUE 3.314 REJECTION LEVEL 0.050
STANDARD ERRORS AND CRITICAL VALUES OF DIFFERENCES

# *Appendix E. Odds Ratios for the Kinetic Index Metric*

**Kinetic Index Groupings**

**Low Exposures**
Electrical Engineer (30/613)
Nonelectrical worker (2234/64547)
Phone line worker and splicer (4/31) *[2268/65191]*

**Medium Exposures**
Electrician and apprentice (28/728)
Motion picture projectionist (1/22)
EE Technician (24/521) *[53/1271]*

**High Exposures**
TV and radio repairman (4/106)
Electric power wire and cable worker (2/50)
Welder and flamer cutter (27/579)
Power station operator (1/15) *[34/750]*

$$\text{CaseControl\_Ratio}_{LO} := \frac{2268}{65191}$$

$$\text{CaseControl\_Ratio}_{MED} := \frac{53}{1271}$$

$$\text{CaseControl\_Ratio}_{HI} := \frac{34}{750}$$

$$\text{OR}_{LO} := \frac{\text{CaseControl\_Ratio}_{LO}}{\text{CaseControl\_Ratio}_{LO}} \qquad \text{OR}_{LO} = 1$$

$$\text{OR}_{MED} := \frac{\text{CaseControl\_Ratio}_{MED}}{\text{CaseControl\_Ratio}_{LO}} \qquad \text{OR}_{MED} = 1.199$$

$$\text{OR}_{HI} := \frac{\text{CaseControl\_Ratio}_{HI}}{\text{CaseControl\_Ratio}_{LO}} \qquad \text{OR}_{HI} = 1.303$$

| | D | $\bar{D}$ | |
|---|---|---|---|
| E | A | B | $N_1$ |
| $\bar{E}$ | C | D | $N_2$ |
| | $M_1$ | $M_2$ | T |

$$\chi_{sq}(A, M_1, M_2, N_1, N_2, T) := \frac{\left(A - \frac{N_1 \cdot M_1}{T}\right)^2}{\left[\frac{N_1 \cdot N_2 \cdot M_1 \cdot M_2}{T^2 \cdot (T-1)}\right]}$$

$$\text{chi}_{MED} := \chi_{sq}(53, 2321, 66462, 1324, 67459, 68783)$$

$$\text{chi}_{HI} := \chi_{sq}(34, 2302, 65941, 784, 67459, 68243)$$

$$\text{CI}_{lower}(Z, \text{chi\_square}, OR) := OR^{\left(1 - \frac{Z}{\sqrt{\text{chi\_square}}}\right)}$$

$$\text{CI}_{upper}(Z, \text{chi\_square}, OR) := OR^{\left(1 + \frac{Z}{\sqrt{\text{chi\_square}}}\right)}$$

$$\text{CI}_{lower}(1.96, \text{chi}_{MED}, \text{OR}_{MED}) = 0.9081$$

$$\text{CI}_{upper}(1.96, \text{chi}_{MED}, \text{OR}_{MED}) = 1.5821$$

$$\text{CI}_{lower}(1.96, \text{chi}_{HI}, \text{OR}_{HI}) = 0.9227$$

$$\text{CI}_{upper}(1.96, \text{chi}_{HI}, \text{OR}_{HI}) = 1.8403$$

# *Appendix F. Odds Ratios for Average Magnetic Field Measurements*

**Average Magnetic Field Groupings**

**Low Exposures**
Electrical Engineer (30/613)
Nonelectrical worker (2234/64547)
Phone line worker and splicer (4/31) *[2268/65191]*

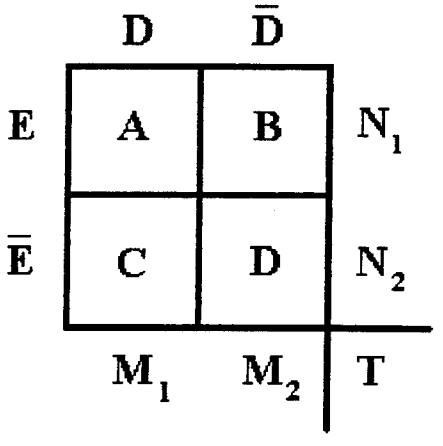
**Medium Exposures**
Electrician and apprentice (28/728)
TV and radio repairman (4/106)
EE Technician (24/521) *[58/1355]*

**High Exposures**
Motion picture projectionist (1/22)
Electric power wire and cable worker (2/50)
Welder and flamer cutter (27/579)
Power station operator (1/15) *[31/666]*

$$\text{CaseControl\_Ratio}_{LO} := \frac{2268}{65191}$$

$$\text{CaseControl\_Ratio}_{MED} := \frac{58}{1355}$$

$$\text{CaseControl\_Ratio}_{HI} := \frac{31}{666}$$




$$OR_{LO} := \frac{\text{CaseControl\_Ratio}_{LO}}{\text{CaseControl\_Ratio}_{LO}} \qquad OR_{LO} = 1$$

$$OR_{MED} := \frac{\text{CaseControl\_Ratio}_{MED}}{\text{CaseControl\_Ratio}_{LO}} \qquad OR_{MED} = 1.23$$

$$OR_{HI} := \frac{\text{CaseControl\_Ratio}_{HI}}{\text{CaseControl\_Ratio}_{LO}} \qquad OR_{HI} = 1.338$$

$$\chi_{sq}(A, M_1, M_2, N_1, N_2, T) := \frac{\left(A - \frac{N_1 \cdot M_1}{T}\right)^2}{\left[\frac{N_1 \cdot N_2 \cdot M_1 \cdot M_2}{T^2 \cdot (T-1)}\right]}$$

$$chi_{MED} := \chi_{sq}(58, 2326, 66546, 1413, 67459, 68872)$$

$$chi_{HI} := \chi_{sq}(31, 2299, 65857, 697, 67459, 68156)$$

$$CI_{lower}(Z, chi\_square, OR) := OR^{\left(1 - \frac{Z}{\sqrt{chi\_square}}\right)}$$

$$CI_{upper}(Z, chi\_square, OR) := OR^{\left(1 + \frac{Z}{\sqrt{chi\_square}}\right)}$$

$$CI_{lower}(1.96, chi_{MED}, OR_{MED}) = 0.9433$$

$$CI_{upper}(1.96, chi_{MED}, OR_{MED}) = 1.6047$$

$$CI_{lower}(1.96, chi_{HI}, OR_{HI}) = 0.9322$$

$$CI_{upper}(1.96, chi_{HI}, OR_{HI}) = 1.9202$$

# *Appendix G. Mathcad Parameter Fitting Routine*

Experimental fit procedure for the kinetic model.

The basic model equation for the [Y] concentration level is:

$$f(t,x_0,y_0,k_1,k_2,k_3) := \frac{k_1}{k_3} + \frac{k_1 - k_2 \cdot x_0}{k_2 - k_3} \cdot \exp(-k_2 \cdot t) + \frac{k_2 \cdot (k_1 - k_3 \cdot x_0) - y_0 \cdot k_3 \cdot (k_2 - k_3)}{-k_3 \cdot (k_2 - k_3)} \cdot \exp(-k_3 \cdot t)$$

Note that there is no scaling included.

The corresponding equation for the [X] concentration level is:

$$g(t,x_0,k_1,k_2) := \frac{k_1}{k_2} + \frac{k_2 \cdot x_0 - k_1}{k_2} \cdot \exp(-k_2 \cdot t)$$

For the curve fitting we will use a more complicated conditional that takes both response curves and puts them in successive time intervals. We also force consistency in the initial conditions this way. The scaling to set ambient steady-state to 1 is included.

$$fit(t,p_1,p_2,p_3,p_4,p_5,p_6) := \begin{cases} f\left(t, \frac{p_4}{p_5}, \frac{p_4}{p_6}, p_1, p_2, p_3\right) \cdot \frac{p_6}{p_4} & \text{if } t<260 \\ \text{otherwise} \\ \quad x0 \leftarrow g\left(20, \frac{p_4}{p_5}, p_1, p_2\right) \\ \quad y0 \leftarrow f\left(20, \frac{p_4}{p_5}, \frac{p_4}{p_6}, p_1, p_2, p_3\right) \\ \quad f(t-280, x0, y0, p_4, p_5, p_6) \cdot \left(\frac{p_6}{p_4}\right) \end{cases}$$

The curve fit routine requires a vector function that returns the function value at time t plus the partial derivatives of the function with respect to all the parameters. Here we'll use a numerical approximation for the derivatives.

$$D(t,p) := \left| \begin{array}{l} p1 \leftarrow p_0 \\ p2 \leftarrow p_1 \\ p3 \leftarrow p_2 \\ p4 \leftarrow p_3 \\ p5 \leftarrow p_4 \\ p6 \leftarrow p_5 \\ \left[ \begin{array}{l} fit(t,p1,p2,p3,p4,p5,p6) \\ \frac{d}{dp1} fit(t,p1,p2,p3,p4,p5,p6) \\ \frac{d}{dp2} fit(t,p1,p2,p3,p4,p5,p6) \\ \frac{d}{dp3} fit(t,p1,p2,p3,p4,p5,p6) \\ \frac{d}{dp4} fit(t,p1,p2,p3,p4,p5,p6) \\ \frac{d}{dp5} fit(t,p1,p2,p3,p4,p5,p6) \\ \frac{d}{dp6} fit(t,p1,p2,p3,p4,p5,p6) \end{array} \right] \end{array} \right.$$

Now we furnish the data from Lin, et al., 1995 in order to start the curve fit.

$$t_{dat} := (10 \;\; 20 \;\; 60 \;\; 120 \;\; 280 \;\; 320 \;\; 380 \;\; 440 \;\; 680)^T$$

$$x_{dat} := (1.25 \;\; 1.35 \;\; 1.07 \;\; 1.05 \;\; 1.37 \;\; 1.35 \;\; 1.23 \;\; 1.03 \;\; 0.95)^T$$

The first four are the unswitched curve, the last five are the decay part of the switched curve.

$j1 := 0..3 \qquad j2 := 4..8$

Now we furnish initial guesses for the parameter values. $p_{ini} := \left(\frac{1}{10} \;\; \frac{1}{15} \;\; \frac{1}{20} \;\; \frac{1}{200} \;\; \frac{1}{500} \;\; \frac{1}{350}\right)^T$

And now the actual fit.

$p := genfit(t_{dat}, x_{dat}, p_{ini}, D)$

*Genfit* is a least squares curve fitter using a gradient search method to find the parameters that minimize mean squared errors.

$$p = \begin{bmatrix} 9.7389989672 \cdot 10^{-2} \\ 5.7503070511 \cdot 10^{-2} \\ 5.7414877317 \cdot 10^{-2} \\ 5.0934546457 \cdot 10^{-3} \\ 1.5608371301 \cdot 10^{-3} \\ 3.0573859279 \cdot 10^{-3} \end{bmatrix}$$

**Figure 9 shows the graph resulting from these parameters.**

## *Appendix H. Simultaneous Equation Solver for Parameters in Appendix G*

In Appendix G parameters were defined in a way which was easier for Mathcad to use its genfit function. $k_1$, $k_1$*, $k_2$, $k_2$*, $k_3$, and $k_3$* are $p_4$, $p_1$, $p_5$, $p_2$, $p_6$, $p_3$ respectively in Appendix G. In order to get the full picture, however, k1, k2, k3, $\delta k_1$, $\delta k_2$, and $\delta k_3$ need to be separated out of the starred variables and defined in terms of a 4 mG ambient magnetic field which was used in Lin, et al., 1995. Below, a=ambient, or the unstarred variables above, and e=accelerated, or the starred variables above.

$k_{1a} := 5.0934546457 \cdot 10^{-3}$ $k_{2a} := 1.5608371301 \cdot 10^{-3}$ $k_{3a} := 3.0573859279 \cdot 10^{-3}$

$k_{1e} := 9.7389989672 \cdot 10^{-2}$ $k_{2e} := 5.7503070511 \cdot 10^{-2}$ $k_{3e} := 5.7414877317 \cdot 10^{-2}$

$B_a := 4$ Ambient magnetic field magnitude, Lin, et al., 1995.

$B_e := \frac{8}{0.1}$ $B_e = 80$ Experimentally applied exogenous magnetic field magnitude, Lin, et al., 1995.

Initial guesses for parameter values which can be inserted directly into equations 4 and 5.

$k_{1o} := 0$ $k_{2o} := 0$ $k_{3o} := 0$

$\delta k_1 := 0$ $\delta k_2 := 0$ $\delta k_3 := 0$

Given

$k_{1a} = k_{1o} + B_a \cdot \delta k_1$ $k_{1e} = k_{1o} + B_e \cdot \delta k_1$

$k_{2a} = k_{2o} + B_a \cdot \delta k_2$ $k_{2e} = k_{2o} + B_e \cdot \delta k_2$

$k_{3a} = k_{3o} + B_a \cdot \delta k_3$ $k_{3e} = k_{3o} + B_e \cdot \delta k_3$

$$\text{Find}(k_{1o}, \delta k_1, k_{2o}, \delta k_2, k_{3o}, \delta k_3) = \begin{bmatrix} 2.3574227589 \cdot 10^{-4} \\ 1.2144280925 \cdot 10^{-3} \\ -1.3834909426 \cdot 10^{-3} \\ 7.3608201817 \cdot 10^{-4} \\ 1.9646532847 \cdot 10^{-4} \\ 7.1523014986 \cdot 10^{-4} \end{bmatrix}$$

**Final Parameter Values**

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# Vita

Timothy W. Crosnoe [redacted], but resided in Cape Girardeau, Missouri for the majority of his early life. His parents are Clifford and Sally Crosnoe of Cape Girardeau, Missouri, and his wife, Kristin, is from Rolla, Missouri. In 1988 Captain Crosnoe graduated cum laude from the University of Missouri at Rolla, Missouri with a bachelor of science degree in electrical engineering. Upon graduation, he was commissioned and assigned to Newark AFB, Ohio where he was the energy manager for the Aerospace Guidance and Metrology Center. In January of 1993 Captain Crosnoe was reassigned to Whiteman AFB, Missouri where he filled the position of Maintenance Engineer for the 509th Civil Engineering Squadron. In October of 1993 he passed the Principles and Practice of Engineering Examination to become a registered Professional Engineer in the state of Missouri. In 1994 Captain Crosnoe began attending the Air Force Institute of Technology where he will complete a master of science degree in engineering and environmental management in December 1995.

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13. ABSTRACT (Maximum 200 words)

It is a well known fact that high frequency, or radio frequency, radiation can be directly harmful to biological tissue. The radiation frequencies to which humans are most exposed, however, are the extremely low frequencies, or ELFs. To date there has been no definitive measure for predicting the ability of low frequency electromagnetic radiation to cause adverse biological effects. Two specific measures, average magnetic field and kinetic index, have been used in studies to determine if they are useful predictors of adverse effects, specifically leukemia. Unfortunately, both have shown only marginal results.

This thesis analyzed and improved the kinetic index measure (Thomas, et al., 1994) by utilizing laboratory biological data to increase the validity of the parameters of an existing model. Then, using this "improved" model, raw magnetic field exposure data from a previous study was analyzed and compared with the measurement method used in that study (average magnetic field).

The results of the model modification showed that accurate modeling of the existing laboratory data could only be accomplished by including and additional parameter to the existing Litovitz multistage model. The results of the model application, however, were not particularly conclusive. The case-control study used for the model application was less than ideal, requiring that more rigorous epidemiological studies be conducted in order to accurately test the improved model.

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